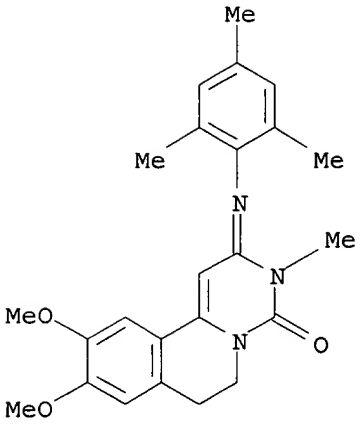


● HCl

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

18 REFERENCES IN FILE CA (1962 TO DATE)
18 REFERENCES IN FILE CAPLUS (1962 TO DATE)

```
=> sel 1-2 rn name
      1 ANSWERS ARE AVAILABLE.  SPECIFIED ANSWER NUMBER EXCEEDS ANSWER SET SIZE.
The answer numbers requested are not in the answer set.
ENTER ANSWER NUMBER OR RANGE (1-):1
E1 THROUGH E3 ASSIGNED

=> sel 2 rn name
      1 ANSWERS ARE AVAILABLE.  SPECIFIED ANSWER NUMBER EXCEEDS ANSWER SET SIZE.
The answer numbers requested are not in the answer set.
ENTER ANSWER NUMBER OR RANGE (1-):end

=> sel l1 rn name
E4 THROUGH E5 ASSIGNED

=> fil medl capl biosis uspatful
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                17.96      18.17

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FILE 'CAPLUS' ENTERED AT 11:33:15 ON 10 JAN 2003
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FILE 'USPATFULL' ENTERED AT 11:33:15 ON 10 JAN 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)
```

```
=> s e1-5
L3          271 ("HL 725"/BI OR "TREQUINSIN HYDROCHLORIDE"/BI OR 78416-81-6/BI
                OR TREQUINSIN/BI OR 79855-88-2/BI)

=> s memory or learning or perception or depression or dementia
L4      1461951 MEMORY OR LEARNING OR PERCEPTION OR DEPRESSION OR DEMENTIA

=> s l3 and l4
L5           12 L3 AND L4

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6           12 DUP REM L5 (0 DUPLICATES REMOVED)

=> d ibib abs kwic 10-12

L6   ANSWER 10 OF 12  USPATFULL
ACCESSION NUMBER:         2000:31420  USPATFULL
TITLE:                    Local administration of phosphodiesterase inhibitors
                          for the treatment of erectile dysfunction
INVENTOR(S):              Doherty, Jr., Paul C., Cupertino, CA, United States
                          Place, Virgil A., Kawaihae, HI, United States
                          Smith, William L., Mahwah, NJ, United States
PATENT ASSIGNEE(S):       Vivus, Inc., Mountain View, CA, United States (U.S.
                          corporation)

                               NUMBER         KIND    DATE
                          ---------------- ------ --------
PATENT INFORMATION:       US 6037346               20000314
APPLICATION INFO.:        US 1998-181070           19981027  (9)
RELATED APPLN. INFO.:     Continuation-in-part of Ser. No. US 1997-958816, filed
                          on 28 Oct 1997, now abandoned
DOCUMENT TYPE:            Utility
FILE SEGMENT:             Granted
PRIMARY EXAMINER:         Reamer, James H.
LEGAL REPRESENTATIVE:     Reed, Dianne E.Reed & Associates
NUMBER OF CLAIMS:         94
EXEMPLARY CLAIM:          1,23
NUMBER OF DRAWINGS:       1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT:               1331
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      A method is provided for treating erectile dysfunction in a mammalian
        male individual. The method involves the local administration of a
        phosphodiesterase inhibitor or a pharmaceutically acceptable salt,
        ester, amide or derivative thereof within the context of an effective
        dosing regimen. A preferred mode of administration is transurethral.
        Pharmaceutical formulations and kits are provided as well.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM    . . . literature for a variety of therapeutic uses, including
        treatment of obstructive lung disease, allergies, hypertension, angina,
        congestive heart failure and depression (see, e.g., Goodman
        and Gilman's The Pharmacological Basis of Therapeutic Ninth Edition,
        Chapter 34). Oral and parenteral administration of phosphodiesterase.
        .
DETD    . . . 5-methyl-imazodan, indolidan and ICI1118233, quinolinone
        compounds such as cilostamide, cilostazol and vesnarinone, and other
        molecules such as bemoradan, anergrelide, siguazodan, trequinsin
        , pimobendan, SKF-94120, SKF-95654, lixazinone and isomazole.

L6   ANSWER 11 OF 12  USPATFULL
ACCESSION NUMBER:         1999:160044  USPATFULL
```

TITLE: Compounds and methods for treating PDE IV-related diseases

INVENTOR(S): Barnette, Mary S., West Chester, PA, United States
Torphy, Theodore J., Bryn Mawr, PA, United States
Christensen, IV, Siegfried Benjamin, Philadelphia, PA, United States

PATENT ASSIGNEE(S): SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 5998428 | | 19991207 |
| APPLICATION INFO.: | US 1997-944044 | | 19970903 (8) |

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-456274, filed on 31 May 1995 which is a continuation of Ser. No. WO 1994-US6861, filed on 17 Jun 1994

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: MacMillan, Keith D.
LEGAL REPRESENTATIVE: Kanagy, James M, Kinzig, Charles M
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 826

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to a method for selecting PDE IV inhibitors which have a salutory therapeutic index, and to compounds having these properties.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . nausea and emesis. Indications are that side effects of denbufylline, another PDE IV inhibitor targeted for the treatment of multi-infarct **dementia**, may include pyrosis, nausea and emesis as well. These side effects are thought to occur as a result of inhibiting. . .

SUMM . . . 0.110 1.1
methoxyphenyl)cyclohexan-1-carboxylate]
cis-[4-cyano-4-(3-cyclopropylmethoxy-4- 0.021 0.04 2.0
difluoromethoxyphenyl)cyclohexan-1-ol]
(R)-(+)-ethyl[4-(3-cyclopentyloxy-4- 0.14 0.3 2.143
methoxyphenyl)pyrrolidine-2-
ylidene]acetate
2-carbomethoxy-4-cyano-4-(3- 0.140 0.5 3.571
cyclopropylmethoxy-4-
difluoromethoxyphenyl)cyclohexan-1-one
**trequinsin** 1.6 5.0 3.125
dipyridamole 5.2 32.5 6.25

---

SUMM Denbufylline is 7-acetonyl,1,3-dibutylxanthine made by SmithKline Beecham. Papaverine is 1 -[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline. **Trequinsin** is 2,3,6,7-tetrahydro-2-(mesitylimino)-9,10-dimethoxy-3-methyl-4H-primido[6,1-.alpha.]isoquinoline-4-one. Dipyrimadole is the generic name for 2,2',2"2'"-[(4,8-dipiperidinopyrimido[5,4-d]pyrimidine-2-6-diyl)dinitrilo]tetraethanol.

SUMM . . . IC.sub.50 ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0. Preferred compounds are **trequinsin**, dipyridamole, and papaverine. Compounds such as cis-[cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylate], 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, and cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol] are examples of structures which bind preferentially to the low. . .

L6 ANSWER 12 OF 12 USPATFULL

ACCESSION NUMBER: 1999:128527 USPATFULL

TITLE: Method of inducing vasorelaxation to treat pulmonary hypertension

INVENTOR(S): Lawson, Charles A., Verona, NJ, United States
Pinsky, David J., Riverdale, NY, United States
Smerling, Arthur, New Rochelle, NY, United States
Stern, David M., Great Neck, NY, United States

PATENT ASSIGNEE(S): The Trustees of Columbia University in the City of New York, New York, NY, United States (U.S. corporation)

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 5968911 | | 19991019 | |
| | WO 9509636 | | 19950413 | |
| APPLICATION INFO.: | US 1997-362571 | | 19970218 | (8) |
| | WO 1994-US11248 | | 19941004 | |
| | | | 19970218 | PCT 371 date |
| | | | 19970218 | PCT 102(e) date |

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1993-131984, filed on 4 Oct 1993

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted

PRIMARY EXAMINER: Kunz, Gary L.

LEGAL REPRESENTATIVE: White, John P.Cooper & Dunham LLP

NUMBER OF CLAIMS: 47

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 19 Drawing Figure(s); 31 Drawing Page(s)

LINE COUNT: 1790

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a method of selectively decreasing pulmonary vascular resistance in a subject by administering endobronchially a drug chosen from among cAMP analogs, cGMP analogs, phosphodiesterase inhibitors, nitric oxide precursors, nitric oxide donors, and nitric oxide analogs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Family II - **Trequinsin (HL 725)**.

DETD . . . increased slightly following 8-Br-cGMP (FIGS. 4A-4H), data of others (11-14) suggests that stimulation of the NO pathway may result in **depression** of myocardial contractility, which would be of clinical concern in patients with compromised ventricular function. The effect of inhaled 8-Br-cGMP. . .

DETD . . . of the nitric oxide pathway might depress myocardial contractility, which would be of clinical concern in patients with cor pulmonale. **Depression** of myocardial contractility has been ascribed to nitric oxide production (11-13), and 8-Br-cGMP itself has been shown to exert a. . .

DETD . . . establishment of pulmonary hypertension by infusion of the thromboxane A.sub.2 analog (data not shown). This is in contrast to the **depression** of myocardial contractility observed following intravenous administration of a known negative inotrope.sup.17 (esmolol, 1 mg/kg; FIG. 19C).

DETD It has been suggested that stimulation of the NO pathway may result in **depression** of myocardial contractility,.sup.11-14 which would be of clinical concern in patients with compromised ventricular function. **Depression** of myocardial contractility has been ascribed to nitric oxide production,.sup.11-13 and 8-Br-cGMP itself has been shown to exert a moderate. . .

```
=> s pde 2 or phosphodiesterase 2 or pde II or phosphodiesterase II
L7        1025 PDE 2 OR PHOSPHODIESTERASE 2 OR PDE II OR PHOSPHODIESTERASE II

=> s memor? or learn? or cognit? or percept? or dement? or alzheimer or vision? or
visual? or speech?
L8     2097171 MEMOR? OR LEARN? OR COGNIT? OR PERCEPT? OR DEMENT? OR ALZHEIMER
               OR VISION? OR VISUAL? OR SPEECH?

=> s l8 and l7
L9         111 L8 AND L7

=> s l8 (S) l7
L10         17 L8 (S) L7

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11          13 DUP REM L10 (4 DUPLICATES REMOVED)

=> d ibib abs kwic 10-13

L11  ANSWER 10 OF 13     MEDLINE                          DUPLICATE 3
ACCESSION NUMBER:   83163353     MEDLINE
DOCUMENT NUMBER:    83163353   PubMed ID: 6300356
TITLE:              Cyclic adenosine 3':5'-monophosphate phosphodiesterase and
                    its role in learning in Drosophila.
AUTHOR:             Shotwell S L
CONTRACT NUMBER:    GM-07616 (NIGMS)
SOURCE:             JOURNAL OF NEUROSCIENCE, (1983 Apr) 3 (4) 739-47.
                    Journal code: 8102140. ISSN: 0270-6474.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        198305
ENTRY DATE:         Entered STN: 19900318
                    Last Updated on STN: 19970203
                    Entered Medline: 19830527
AB   Drosophila carrying the X-linked mutation dunce (dnc) showed poor
     learning in a negative reinforcement olfactory conditioning
     paradigm (Dudai, Y., Y.-N. Jan, D. Byers, W.G. Quinn, and S. Benzer (1976)
     Proc. Natl. Acad. Sci. U.S.A. 73: 1684-1688). More recently, dnc flies
     were shown to have reduced activity for one of two cAMP phosphodiesterases
     (PDEs) present in normal flies, PDE II, whereas PDE
     form I was unaffected (Byers, D., R. L. Davis, and J. A. Kiger, Jr. (1981)
     Nature 289: 79-81). A micro-assay technique is described that allows the
     separate measurement of PDE I and PDE II in crude
     extracts, based on specific inhibition of PDE I [3H]cAMP hydrolysis by
     cGMP. Using this technique, PDE II is shown to occur
     normally at high specific activity in the nervous system, consistent with
     the hypothesis that this enzyme plays a role in neuronal function. Reduced
     PDE II activity correlates with poor learning
     in dnc flies at three developmental stages (first and third instar larva
     and adult), as well as in response to genetic modification of dnc gene
     activity. Biochemical and genetic experiments fail to reveal any abnormal
     regulation of PDE II in dnc. The specific activity of
     PDE II is shown to correlate in a one to one fashion
     with the level of normal dnc gene (dnc+) activity at five different doses
     of dnc+. These results support the hypothesis that PDE
     II represents the primary product of the dnc gene, indicating a
     role for this enzyme in Drosophila learning.
AB   Drosophila carrying the X-linked mutation dunce (dnc) showed poor
     learning in a negative reinforcement olfactory conditioning
```

paradigm (Dudai, Y., Y.-N. Jan, D. Byers, W.G. Quinn, and S. Benzer (1976) Proc.. . . recently, dnc flies were shown to have reduced activity for one of two cAMP phosphodiesterases (PDEs) present in normal flies, **PDE II**, whereas PDE form I was unaffected (Byers, D., R. L. Davis, and J. A. Kiger, Jr. (1981) Nature 289: 79-81). A micro-assay technique is described that allows the separate measurement of PDE I and **PDE II** in crude extracts, based on specific inhibition of PDE I [3H]cAMP hydrolysis by cGMP. Using this technique, **PDE II** is shown to occur normally at high specific activity in the nervous system, consistent with the hypothesis that this enzyme plays a role in neuronal function. Reduced **PDE II** activity correlates with poor **learning** in dnc flies at three developmental stages (first and third instar larva and adult), as well as in response to genetic modification of dnc gene activity. Biochemical and genetic experiments fail to reveal any abnormal regulation of **PDE II** in dnc. The specific activity of **PDE II** is shown to correlate in a one to one fashion with the level of normal dnc gene (dnc+) activity at five different doses of dnc+. These results support the hypothesis that **PDE II** represents the primary product of the dnc gene, indicating a role for this enzyme in Drosophila **learning**.

L11 ANSWER 11 OF 13 MEDLINE
ACCESSION NUMBER: 83225651 MEDLINE
DOCUMENT NUMBER: 83225651 PubMed ID: 6305023
TITLE: Gain, speed and sensitivity of GTP binding vs PDE activation in visual excitation.
AUTHOR: Liebman P A; Pugh E N Jr
CONTRACT NUMBER: EY00012 (NEI)
EY00102 (NEI)
EY01583 (NEI)
SOURCE: VISION RESEARCH, (1982) 22 (12) 1475-80.
Journal code: 0417402. ISSN: 0042-6989.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198307
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19830708

AB About 2000 PDE molecules are gradually activated by one bleached rhodopsin molecule, R* on a toad disk membrane to yield a final enzyme velocity of about 2.5 x 10(6) cGMP hydrolyzed sec-1 bleached rhodopsin-1. This amplified effect of a single photon requires GTP, whose function we originally proposed (Yee and Liebman, 1978; Liebman and Pugh, 1979) to serve as a "**memory**" label attached to each PDE as it is contacted via lateral diffusion by R*. Thus, the binding of GTP was explicitly seen as an identically-amplified casual link in the amplified PDE activation. We have subjected our GTP-PDE coupling hypothesis to both stoichiometric and kinetic tests using radioactive GTP labelling techniques. We find agreement in principle with our original hypothesis with modifications to allow for (1) GTP binding to a separate G-protein (gamma) which activates **PDE**; (2) evidence that there are fewer PDE's activated than GTP's bound in response to a light flash; (3) evidence of reversible binding of gamma to PDE with incomplete activation of the latter; (4) multisecond delay of GTP binding compatible with lateral diffusionally-mediated activation of thousands of gamma's by single R*'s; (5) gain regulation by ATP that reduces both PDE activation and GTP binding.
AB . . . photon requires GTP, whose function we originally proposed (Yee and Liebman, 1978; Liebman and Pugh, 1979) to serve as a "**memory**

" label attached to each PDE as it is contacted via lateral diffusion by R*. Thus, the binding of GTP was. . . principle with our original hypothesis with modifications to allow for (1) GTP binding to a separate G-protein (gamma) which activates **PDE**; (**2**) evidence that there are fewer PDE's activated than GTP's bound in response to a light flash; (3) evidence of reversible. . .

L11 ANSWER 12 OF 13 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 83009254 MEDLINE
DOCUMENT NUMBER: 83009254 PubMed ID: 6288893
TITLE: Defective cyclic adenosine 3':5'-monophosphate phosphodiesterase in the Drosophila memory mutant dunce.
AUTHOR: Kauvar L M
SOURCE: JOURNAL OF NEUROSCIENCE, (1982 Oct) 2 (10) 1347-58. Journal code: 8102140. ISSN: 0270-6474.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198212
ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 19970203
Entered Medline: 19821203

AB A detailed characterization of the cyclic nucleotide phosphodiesterase (PDEs) from normal Drosophila melanogaster was made, including purification of the two major enzymes to near homogeneity. A third more labile phosphodiesterase also was identified in crude homogenates. The total activity per fly of one of these three enzymes, **PDE-II**, is strongly influenced by the dunce locus. Two independently derived dunce mutants produce variations of **PDE-II** with modified intrinsic properties: a marked decrease of thermal stability in dunce and a 10-fold increase in the Michaelis kinetic constant in dunce. These defects, which persisted in purified preparations of **PDE-II**, were mapped genetically to dunce. The results support the identification of dunce as the structural locus for **PDE-II**. The tight connection between the dunce gene and the **PDE-II** enzyme indicates that defective cyclic adenosine 3':5'-monophosphate metabolism is the primary lesion which leads to failure of dunce flies to **learn** in the olfactory associative conditioning paradigm of Quinn et al. (Quinn, W. G., W. A. Harris, and S. Benzer (1974) Proct. Natl. Acad. Sci. U. S. A. 71: 708-712).

AB . . . more labile phosphodiesterase also was identified in crude homogenates. The total activity per fly of one of these three enzymes, **PDE-II**, is strongly influenced by the dunce locus. Two independently derived dunce mutants produce variations of **PDE-II** with modified intrinsic properties: a marked decrease of thermal stability in dunce and a 10-fold increase in the Michaelis kinetic constant in dunce. These defects, which persisted in purified preparations of **PDE-II**, were mapped genetically to dunce. The results support the identification of dunce as the structural locus for **PDE-II**. The tight connection between the dunce gene and the **PDE-II** enzyme indicates that defective cyclic adenosine 3':5'-monophosphate metabolism is the primary lesion which leads to failure of dunce flies to **learn** in the olfactory associative conditioning paradigm of Quinn et al. (Quinn, W. G., W. A. Harris, and S. Benzer (1974). . .

L11 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:98116 CAPLUS
DOCUMENT NUMBER: 94:98116
TITLE: Flow of information in the light-triggered cyclic nucleotide cascade of vision

AUTHOR(S): Fung, Bernard K. K.; Hurley, James B.; Stryer, Lubert
CORPORATE SOURCE: Sch. Med., Stanford Univ., Stanford, CA, 94305, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1981), 78(1), 152-6
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Photolyzed rhodopsin (I) catalyzes the exchange of GTP for GDP bound to a protein in retinal rod outer segments. It has been previously proposed that the GTP complex of this protein regulates cyclic GMP **phosphodiesterase** (**II**) and that it may be the 1st amplified intermediate in **visual** excitation. The identification and characterization of transducin (III), a regulatory protein consisting of 3 kinds of polypeptide chains, III.alpha. (39 kilodaltons), III.beta. (36 kilodaltons), and III.gamma. (.apprx.10 kilodaltons), is reported. Reconstituted membranes contg. I and III, but no II, exhibited GTPase activity and amplified the binding of guanosine 5'-(.beta.,.gamma.-imido)triphosphate (IV), a nonhydrolyzable analog of GTP, on illumination. A single photolyzed I mol. led to the uptake of IV by 71 mols. of III. High-pressure liq. chromatog. showed that the binding site for GTP is on the .alpha. subunit of III. II on unilluminated disk membranes could be fully activated by addn. of III.alpha. contg. bound IV. These findings strongly suggest that III is the 1st amplified information-carrying intermediate in the cyclic nucleotide cascade of vision.

AB Photolyzed rhodopsin (I) catalyzes the exchange of GTP for GDP bound to a protein in retinal rod outer segments. It has been previously proposed that the GTP complex of this protein regulates cyclic GMP **phosphodiesterase** (**II**) and that it may be the 1st amplified intermediate in **visual** excitation. The identification and characterization of transducin (III), a regulatory protein consisting of 3 kinds of polypeptide chains, III.alpha. (39 kilodaltons), III.beta. (36 kilodaltons), and III.gamma. (.apprx.10 kilodaltons), is reported. Reconstituted membranes contg. I and III, but no II, exhibited GTPase activity and amplified the binding of guanosine 5'-(.beta.,.gamma.-imido)triphosphate (IV), a nonhydrolyzable analog of GTP, on illumination. A single photolyzed I mol. led to the uptake of IV by 71 mols. of III. High-pressure liq. chromatog. showed that the binding site for GTP is on the .alpha. subunit of III. II on unilluminated disk membranes could be fully activated by addn. of III.alpha. contg. bound IV. These findings strongly suggest that III is the 1st amplified information-carrying intermediate in the cyclic nucleotide cascade of vision.

=> d ibib abs kwic 5-9

L11 ANSWER 5 OF 13 USPATFULL
ACCESSION NUMBER: 2002:243563 USPATFULL
TITLE: Selective **PDE 2** inhibitors as pharmaceuticals for improving **perception**
INVENTOR(S): Boss, Frank-Gerhard, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Hendrix, Martin, Koln, GERMANY, FEDERAL REPUBLIC OF
Konig, Gerhard, Dusseldorf, GERMANY, FEDERAL REPUBLIC OF
Niewohner, Ulrich, Wermelskirchen, GERMANY, FEDERAL REPUBLIC OF
Schlemmer, Karl-Heinz, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Schreiber, Rudy, Menlo Park, CA, UNITED STATES
Van Der Staay, Franz-Josef, Lohmar, GERMANY, FEDERAL REPUBLIC OF
Schauss, Dagmar, Wuppertal, GERMANY, FEDERAL REPUBLIC

OF

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 2002132754 | A1 | 20020919 | |
| APPLICATION INFO.: | US 2001-911277 | A1 | 20010723 | (9) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | DE 2000-10037411 | 20000801 |
| | DE 2001-122893 | 20010511 |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Jeffrey M. Greenman, Vice President, Patents and Licensing, Bayer Corporation, 400 Morgan Lane, West Haven, CT, 06516
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 410
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to the use of selective **phosphodiesterase 2 (PDE 2)** inhibitors for producing pharmaceuticals for improving **perception**, concentration, **learning** and/or **memory**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Selective **PDE 2** inhibitors as pharmaceuticals for improving **perception**

AB The invention relates to the use of selective **phosphodiesterase 2 (PDE 2)** inhibitors for producing pharmaceuticals for improving **perception**, concentration, **learning** and/or **memory**.

SUMM [0001] The invention relates to the use of selective **phosphodiesterase 2 (PDE 2)** inhibitors for producing pharmaceuticals for improving **perception**, concentration, **learning** and/or **memory**.

SUMM [0006] It has now been found, surprisingly, that selective **PDE 2** inhibitors are suitable for producing pharmaceuticals for improving **perception**, concentration, **learning** or **memory**.

SUMM [0009] The selective **PDE 2** inhibitors are particularly suitable for improving **perception**, concentration, **learning** or **memory** after **cognitive** disturbances as occur in particular in situations/diseases/syndromes such as mild **cognitive** impairment, age-associated **learning** and **memory** disturbances, age-associated **memory** losses, vascular **dementia**, craniocerebral trauma, stroke, **dementia** occurring after strokes (post stroke **dementia**), post-traumatic craniocerebral trauma, general disturbances of concentration, disturbances of concentration in children with **learning** and **memory** problems, **Alzheimer**'s disease, **dementia** with Lewy bodies, **dementia** with degeneration of the frontal lobes including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, **dementia** with corticobasal degeneration, amyotrophic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob **dementia**, HIV **dementia**, schizophrenia with **dementia** or Korsakoff psychosis.

CLM What is claimed is:

1. Use of selective **PDE 2** inhibitors for producing

pharmaceuticals for improving **perception**, concentration, **learning** and/or **memory**.

L11 ANSWER 6 OF 13 USPATFULL
ACCESSION NUMBER: 2002:268781 USPATFULL
TITLE: Methods for treatment of cystic fibrosis
INVENTOR(S): Earle, Keith A., North Wales, PA, United States
Alila, Hector W., North Wales, PA, United States
Whitehead, Clark M., Warminster, PA, United States
Thompson, W. Joseph, Doylestown, PA, United States
PATENT ASSIGNEE(S): Cell Pathways, Inc., Horsham, PA, United States (U.S. corporation)

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 6465494 | B1 | 20021015 |
| APPLICATION INFO.: | US 2001-938786 | | 20010824 (9) |

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Dees, Jose' G.
ASSISTANT EXAMINER: Gollamudi, Sharmila S
LEGAL REPRESENTATIVE: Stevenson, Robert W.
NUMBER OF CLAIMS: 37
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 16 Drawing Figure(s); 14 Drawing Page(s)
LINE COUNT: 1944
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Substituted condensation products of N-benzyl-3-indenylacetamides with heterocyclic aldehydes and other such inhibitors are useful for the treatment of cystic fibrosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DRWD FIG. 13 is a **visual** image of immunostaining revealing the expression of **PDE-2** protein in macrophages in the lung of a 39-year old male patient with a known history of cystic fibrosis (60.times.).
DRWD FIG. 15 is a **visual** image of immunostaining revealing the expression of **PDE-2** protein in type II pneumocytes (pulmonary epithelial cells) in the lung of a 39-year old male patient with a known. . .
DETD Human lung tissue samples exhibited positive staining for **PDE-2** and PDE-5 proteins and immunostaining was mostly localized to alveolar and pigment-laden macrophages. FIGS. 13 and 14 are **visual** images of immunostaining to **PDE-2** and PDE-5 proteins, respectively.

L11 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:504946 CAPLUS
DOCUMENT NUMBER: 136:165258
TITLE: Decreased brain levels of 2',3'-cyclic nucleotide-3'-phosphodiesterase in Down syndrome and Alzheimer's disease
AUTHOR(S): Vlkolinsky, R.; Cairns, N.; Fountoulakis, M.; Lubec, G.
CORPORATE SOURCE: Department of Pediatrics, University of Vienna, Vienna, 1090, Austria
SOURCE: Neurobiology of Aging (2001), 22(4), 547-553
CODEN: NEAGDO; ISSN: 0197-4580
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In Down syndrome (DS) as well as in Alzheimer's disease (AD) oligodendroglial and myelin alterations have been reported. 2',3'-cyclic nucleotide-3'-phosphodiesterase (CNPase) and carbonic anhydrase II (CA II) are widely accepted as markers for oligodendroglia and myelin. However, only data on CNPase activity have been available in AD and DS brains so far. In our study we detd. the protein levels of CNPase and CA II in DS, AD and in control post mortem brain samples in order to assess oligodendroglia and myelin alterations in both diseases. We used two dimensional electrophoresis to sep. brain proteins that were subsequently identified by matrix assisted laser desorption and ionization mass-spectroscopy (MALDI-MS). Seven brain areas were investigated (frontal, temporal, occipital and parietal cortex, cerebellum, thalamus and caudate nucleus). In comparison to control brains we detected significantly decreased CNPase protein levels in frontal and temporal cortex of DS patients. The level of CA II protein in DS was unchanged in comparison to controls. In AD brains levels of CNPase were decreased in frontal cortex only. The level of CA II in all brain areas in AD group was comparable to controls. Changes of CNPase protein levels in DS and AD are in agreement with the previous finding of decreased CNPase activity in DS and AD brain. They probably reflect decreased oligodendroglial d. and/or reduced myelination. These can be secondary to disturbances in axon/oligodendroglial communication due to neuronal loss present in both diseases. Alternatively, reduced CNPase levels in DS brains may be caused by impairment of glucose metab. and/or alterations of thyroid functions.

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 60098-35-3, 2',3'-Cyclic nucleotide-3'-**phosphodiesterase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**2**',3'-cyclic nucleotide-3'-phosphodiesterase and carbonic anhydrase II in brain regions in Down syndrome and **Alzheimer**'s disease)

L11 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
ACCESSION NUMBER: 1986:32634 CAPLUS
DOCUMENT NUMBER: 104:32634
TITLE: Phosphodiesterase-probes show distinct defects in rd mice and Irish setter dog disorders
AUTHOR(S): Lee, Rehwa H.; Lieberman, Bernice S.; Hurwitz, Richard L.; Lolley, Richard N.
CORPORATE SOURCE: Sch. Med., Univ. California, Los Angeles, CA, USA
SOURCE: Investigative Ophthalmology & Visual Science (1985), 26(11), 1569-79
CODEN: IOVSDA; ISSN: 0146-0404
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cGMP phosphodiesterase from the visual cells of rd mice and affected Irish setter dogs was analyzed, using biochem., biophys., and immunol. techniques. The mechanisms that cause a deficiency in phosphodiesterase activity in rd mice and Irish setter dogs are distinctly different. Apparently, the phosphodiesterase complex is normal in affected Irish setter dogs but is abnormal in rd mice. The criteria used for detg. the normalcy of the phosphodiesterase complex were sedimentation characteristics, immuno-crossreactivity, and histone-activation, which is a unique characteristic of the visual cell enzyme. According to these criteria, the phosphodiesterase complex in the **visual** cells of rd mice is either absent or abnormal from the onset of **visual** cell differentiation until degeneration, because (1) it exhibits no cross-reactivity with antibody to **phosphodiesterase**; (**2**) it is not activated by histone; and (3), if present, it exhibits abnormal sedimentation characteristics and perhaps subunit structure. Phosphodiesterase from the **visual** cells of affected Irish setter dogs is normal by the same criteria, because (1) it cross-reacts with

antibody against **phosphodiesterase**; (2) it is activated by histone; and (3) it exhibits normal sedimentation and electrophoretic patterns. Depressed levels of phosphodiesterase activity in affected setter photoreceptors are due, perhaps, to a defect in the light-initiated cascade which activates the enzyme normally, in situ.

AB The cGMP phosphodiesterase from the visual cells of rd mice and affected Irish setter dogs was analyzed, using biochem., biophys., and immunol. techniques. The mechanisms that cause a deficiency in phosphodiesterase activity in rd mice and Irish setter dogs are distinctly different. Apparently, the phosphodiesterase complex is normal in affected Irish setter dogs but is abnormal in rd mice. The criteria used for detg. the normalcy of the phosphodiesterase complex were sedimentation characteristics, immuno-crossreactivity, and histone-activation, which is a unique characteristic of the visual cell enzyme. According to these criteria, the phosphodiesterase complex in the **visual** cells of rd mice is either absent or abnormal from the onset of **visual** cell differentiation until degeneration, because (1) it exhibits no cross-reactivity with antibody to **phosphodiesterase**; (2) it is not activated by histone; and (3), if present, it exhibits abnormal sedimentation characteristics and perhaps subunit structure. Phosphodiesterase from the **visual** cells of affected Irish setter dogs is normal by the same criteria, because (1) it cross-reacts with antibody against **phosphodiesterase**; (2) it is activated by histone; and (3) it exhibits normal sedimentation and electrophoretic patterns. Depressed levels of phosphodiesterase activity in affected setter photoreceptors are due, perhaps, to a defect in the light-initiated cascade which activates the enzyme normally, in situ.

L11 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 2

ACCESSION NUMBER: 1985:59697 CAPLUS
DOCUMENT NUMBER: 102:59697
TITLE: Visual learning performance of Drosophila melanogaster is altered by neuropharmaca affecting phosphodiesterase activity and acetylcholine transmission
AUTHOR(S): Folkers, E.; Spatz, H. C.
CORPORATE SOURCE: Inst. Biol. III, Albert-Ludwigs Univ., Freiburg, D-7800, Fed. Rep. Ger.
SOURCE: Journal of Insect Physiology (1984), 30(12), 957-65
CODEN: JIPHAF; ISSN: 0022-1910
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Inhibitors of cyclic nucleotide phosphodiesterases, theophylline and caffeine, decreased visual learning performance in D. melanogaster wild-type C-S. Likewise neostigmine, an inhibitor of acetylcholinesterase, diminished visual learning performance of C-S wild-type flies. The effects of neostigmine as well as theophylline and caffeine on this behavior were reversed by acetylcholine antagonists atropine and d-tubocurarine, whereas atropine and d-tubocurarine at the same concns. do not affect visual learning performance per se. The functional compensation of the effect of phoshodiesterase (PDE) inhibitors by acetylcholine antagonists may be a 1st indication of a functional coupling of cyclic nucleotide metab. and acetylcholine transmission in visual learning performance of Drosophila. The effect of caffeine and the dunce1 mutation are not alike; caffeine reduced **visual** conditioned behavior of the **PDE II** mutant dunce1 further. Moreover visual learning performance of dunce1 was not increased to normal wild type levels by atropine or d-tubocurarine.

AB Inhibitors of cyclic nucleotide phosphodiesterases, theophylline and caffeine, decreased visual learning performance in D. melanogaster wild-type C-S. Likewise neostigmine, an inhibitor of acetylcholinesterase, diminished visual learning performance of C-S

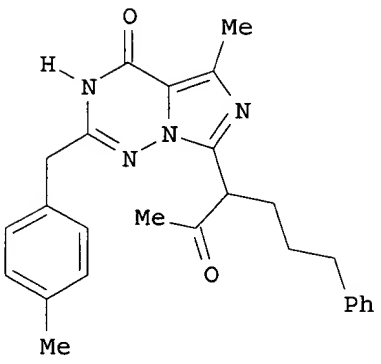
wild-type flies. The effects of neostigmine as well as theophylline and caffeine on this behavior were reversed by acetylcholine antagonists atropine and d-tubocurarine, whereas atropine and d-tubocurarine at the same concns. do not affect visual learning performance per se. The functional compensation of the effect of phoshodiesterase (PDE) inhibitors by acetylcholine antagonists may be a 1st indication of a functional coupling of cyclic nucleotide metab. and acetylcholine transmission in visual learning performance of Drosophila. The effect of caffeine and the dunce1 mutation are not alike; caffeine reduced **visual** conditioned behavior of the **PDE II** mutant dunce1 further. Moreover visual learning performance of dunce1 was not increased to normal wild type levels by atropine or d-tubocurarine.

=> d ibib abs kwic 1-4

L11 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:487565 CAPLUS
DOCUMENT NUMBER: 137:63267
TITLE: Preparation of imidazotriazinones as phosphodiesterase II inhibitors
INVENTOR(S): Niewoehner, Ulrich; Schausz, Dagmar; Hendrix, Martin; Koenig, Gerhard; Boesz, Frank-Gerhard; Van der Staay, Franz-Josef; Schreiber, Rudy; Schlemmer, Karl-Heinz; Grosser, Rolf
PATENT ASSIGNEE(S): Bayer Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002050078 | A1 | 20020627 | WO 2001-EP14450 | 20011210 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10064105 | A1 | 20020627 | DE 2000-10064105 | 20001221 |
| AU 2002016087 | A5 | 20020701 | AU 2002-16087 | 20011210 |
| US 2002198377 | A1 | 20021226 | US 2001-26310 | 20011221 |

PRIORITY APPLN. INFO.: DE 2000-10064105 A 20001221
WO 2001-EP14450 W 20011210
OTHER SOURCE(S): MARPAT 137:63267
GI



II

AB R1CR2R3ZCR6(Z1R5)Z2R7 [I; R1 = (un)substituted Ph, -naphthyl, -(iso)quinolinyl; R2,R3 = H or F; R5 = alkyl; R6 = H or Me; R7 = (un)substituted Ph, -thienyl, -furyl; Z = 3,4-dihydro-4-oxoimidazo[5,1-f][1,2,4]triazin-2,7-diyl; Z1 = CO or CH(OH); Z2 = alk(en)ylene or alkynylene] were prepd. Thus, MeCOCH2CO2Me was alkylated by Ph(CH2)3Br and the reduced and sapond. product amidated by 6-(1-aminoethyl)-(4-methylbenzyl)-1,2,4-triazin-5(4H)-one (prepn. given) and the oxidized product cyclized to give title compd. II. Data for biol. activity of I were given.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Mental disorder
(**dementia**, treatment; prepn. of imidazotriazinones as **phosphodiesterase II** inhibitors)

L11 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:107116 CAPLUS
DOCUMENT NUMBER: 136:145267
TITLE: Selective **phosphodiesterase 2** inhibitors used as medicaments for improving **cognition**
INVENTOR(S): Boss, Frank-Gerhard; Hendrix, Martin; Konig, Gerhard; Niewohner, Ulrich; Schlemmer, Karl-Heinz; Schreiber, Rudy; Van Der Staay, Franz-Josef; Schauss, Dagmar
PATENT ASSIGNEE(S): Bayer Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002009713 | A2 | 20020207 | WO 2001-EP8609 | 20010719 |
| WO 2002009713 | A3 | 20020718 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10122893 A1 20020321 DE 2001-10122893 20010511
US 2002132754 A1 20020919 US 2001-911277 20010723
PRIORITY APPLN. INFO.: DE 2000-10037411 A 20000801
DE 2001-10122893 A 20010511
OTHER SOURCE(S): MARPAT 136:145267
AB The invention discloses the use of selective **phosphodiesterase 2** inhibitors for producing medicaments to improve **cognition**, powers of concn., **learning** capability, and/or **memory** retention.
TI Selective **phosphodiesterase 2** inhibitors used as medicaments for improving **cognition**
AB The invention discloses the use of selective **phosphodiesterase 2** inhibitors for producing medicaments to improve **cognition**, powers of concn., **learning** capability, and/or **memory** retention.
ST **phosphodiesterase 2** inhibitor **cognition** **memory learning** concn
IT **Memory**, biological
(and concn. power; selective **phosphodiesterase 2** inhibitors for improving **cognition**)
IT Mental disorder
(**dementia**; selective **phosphodiesterase 2** inhibitors for improving **cognition**)
IT Mental disorder
(depression; selective **phosphodiesterase 2** inhibitors for improving **cognition**)
IT Brain
(frontal lobe, degeneration; selective **phosphodiesterase 2** inhibitors for improving **cognition**)
IT Anti-**Alzheimer**'s agents
Antiparkinsonian agents
**Cognition** enhancers
Human
**Learning**
(selective **phosphodiesterase 2** inhibitors for improving **cognition**)
IT Brain, disease
(stroke; selective **phosphodiesterase 2** inhibitors for improving **cognition**)
IT Brain, disease
(trauma; selective **phosphodiesterase 2** inhibitors for improving **cognition**)
IT 9036-21-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IV; selective **phosphodiesterase 2** inhibitors for improving **cognition**)
IT 9040-59-9, **Phosphodiesterase II**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; selective **phosphodiesterase 2** inhibitors for improving **cognition**)
IT 7665-99-8, Cyclic GMP 9068-52-4, Phosphodiesterase V
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(selective **phosphodiesterase 2** inhibitors for improving **cognition**)
IT 213324-52-8
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective **phosphodiesterase 2** inhibitors for improving **cognition**)

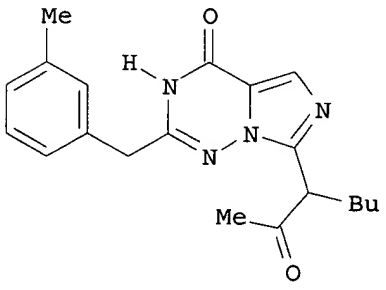
L11 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:669455 CAPLUS

DOCUMENT NUMBER: 137:216964
TITLE: Preparation of imidazotriazinones as PDE-2 inhibitors
INVENTOR(S): Niewoehner, Ulrich; Schauss, Dagmar; Hendrix, Martin; Koenig, Gerhard; Boess, Frank-Gerhard; Van der Staay, Franz-Josef; Schreiber, Rudy; Schlemmer, Karl-Heinz; Moriwaki, Toshiya
PATENT ASSIGNEE(S): Bayer AG, Germany
SOURCE: Ger. Offen., 28 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| DE 10108752 | A1 | 20020905 | DE 2001-10108752 | 20010223 |
| WO 2002068423 | A1 | 20020906 | WO 2002-EP1392 | 20020211 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DE 2001-10108752 A 20010223
OTHER SOURCE(S): MARPAT 137:216964
GI




II

AB R1CR2R3ZCR6R7Z1R5 [I; R1 = (un)substituted Ph; R2,R3 = H or F; R5 = alkyl; Z = 5-alkyl-4-oxoimidazo[5,1-f][1,2,4]triazine-2,7-diyl; Z1 = CO or CH(OH)] were prepd. Thus, 6-(1-aminoethyl)-3-(4-methylbenzyl)-1,2,4-triazin-5(4H)-one was amidated by MeCOCHBuCO2H and the product cyclized to give title compd. II. Data for biol. activity of I were given.
IT Mental disorder
(**dementia**, treatment; prepn. of imidazotriazinones as **PDE-2** inhibitors)

L11 ANSWER 4 OF 13 USPATFULL
ACCESSION NUMBER: 2002:344643 USPATFULL
TITLE: Substituted imidazotriazinones
INVENTOR(S): Niewohner, Ulrich, Wermelskirchen, GERMANY, FEDERAL REPUBLIC OF

Schauss, Dagmar, Solingen, GERMANY, FEDERAL REPUBLIC OF
Hendrix, Martin, Odenthal, GERMANY, FEDERAL REPUBLIC OF
Konig, Gerhard, Dusseldorf, GERMANY, FEDERAL REPUBLIC OF
Boss, Frank-Gerhard, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Staay, Franz-Josef Van Der, Lohmar, GERMANY, FEDERAL REPUBLIC OF
Schreiber, Rudy, Menlo Park, CA, UNITED STATES
Schlemmer, Karl-Heinz, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Grosser, Rolf, Leverkusen, GERMANY, FEDERAL REPUBLIC OF

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 2002198377 | A1 | 20021226 | |
| APPLICATION INFO.: | US 2001-26310 | A1 | 20011221 | (10) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | DE 2000-10064105 | 20001221 |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Jeffrey M. Greenman, Vice President, Patents and Licensing, Bayer Corporation, 400 Morgan Lane, West Haven, CT, 06516
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 1944

AB The present invention relates to new substituted imidazotriazinones, processes for their preparation, and their use for the production of medicaments, in particular for improving perception, concentration power, learning power and/or memory power.

SUMM [0098] Because of their selective **PDE 2** inhibition, the compounds according to the invention are particularly suitable for improving **perception**, concentration power, **learning** power or **memory** power, in particular after **cognitive** disorders, such as occur, for example, in situations/illnesses/syndromes such as mild **cognitive** impairment, age-associated **learning** and **memory** disorders, age-associated **memory** losses, vascular **dementia**, craniocerebral trauma, stroke, **dementia** which occurs after strokes (post-stroke **dementia**), post-traumatic craniocerebral trauma, general concentration disorders, concentration disorders in children with **learning** and **memory** problems, **Alzheimer** 's disease, vascular **dementia**, **dementia** with Lewy bodies, **dementia** with degeneration of the frontal lobes including Pick's disease, Parkinson's disease, progressive nuclear palsy, **dementia** with corticobasal degeneration, amyolateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob **dementia**, HIV **dementia** , schizophrenia with **dementia** or Korsakoff psychosis.

=> d his

(FILE 'HOME' ENTERED AT 11:31:17 ON 10 JAN 2003)

FILE 'REGISTRY' ENTERED AT 11:31:24 ON 10 JAN 2003
L1 1 S TREQUINSIN/CN
L2 1 S HL 725

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                SEL 1-2 RN NAME 1
                SEL L1 RN NAME

     FILE 'MEDLINE, CAPLUS, BIOSIS, USPATFULL' ENTERED AT 11:33:15 ON 10 JAN
     2003
L3           271 S E1-5
L4       1461951 S MEMORY OR LEARNING OR PERCEPTION OR DEPRESSION OR DEMENTIA
L5            12 S L3 AND L4
L6            12 DUP REM L5 (0 DUPLICATES REMOVED)
L7          1025 S PDE 2 OR PHOSPHODIESTERASE 2 OR PDE II OR PHOSPHODIESTERASE I
L8       2097171 S MEMOR? OR LEARN? OR COGNIT? OR PERCEPT? OR DEMENT? OR ALZHEIM
L9           111 S L8 AND L7
L10           17 S L8 (S) L7
L11           13 DUP REM L10 (4 DUPLICATES REMOVED)

=> dup rem l9
PROCESSING COMPLETED FOR L9
L12          106 DUP REM L9 (5 DUPLICATES REMOVED)

=> focus
PROCESSING COMPLETED FOR L12
L13          106 FOCUS L12 1-

=> d ibib abs kwic 6-10

L13  ANSWER 6 OF 106  USPATFULL
ACCESSION NUMBER:        2002:344643  USPATFULL
TITLE:                   Substituted imidazotriazinones
INVENTOR(S):             Niewohner, Ulrich, Wermelskirchen, GERMANY, FEDERAL
                         REPUBLIC OF
                         Schauss, Dagmar, Solingen, GERMANY, FEDERAL REPUBLIC OF
                         Hendrix, Martin, Odenthal, GERMANY, FEDERAL REPUBLIC OF
                         Konig, Gerhard, Dusseldorf, GERMANY, FEDERAL REPUBLIC
                         OF
                         Boss, Frank-Gerhard, Wuppertal, GERMANY, FEDERAL
                         REPUBLIC OF
                         Staay, Franz-Josef Van Der, Lohmar, GERMANY, FEDERAL
                         REPUBLIC OF
                         Schreiber, Rudy, Menlo Park, CA, UNITED STATES
                         Schlemmer, Karl-Heinz, Wuppertal, GERMANY, FEDERAL
                         REPUBLIC OF
                         Grosser, Rolf, Leverkusen, GERMANY, FEDERAL REPUBLIC OF

                              NUMBER         KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 2002198377      A1   20021226
APPLICATION INFO.:       US 2001-26310      A1   20011221  (10)

                                NUMBER         DATE
                         ------------------ --------
PRIORITY INFORMATION:    DE 2000-10064105   20001221
DOCUMENT TYPE:           Utility
FILE SEGMENT:            APPLICATION
LEGAL REPRESENTATIVE:    Jeffrey M. Greenman, Vice President, Patents and
                         Licensing, Bayer Corporation, 400 Morgan Lane, West
                         Haven, CT, 06516
NUMBER OF CLAIMS:        14
EXEMPLARY CLAIM:         1
LINE COUNT:              1944
AB       The present invention relates to new substituted imidazotriazinones,
         processes for their preparation, and their use for the production of
         medicaments, in particular for improving perception,
```

concentration power, **learning** power and/or **memory** power.

AB . . . to new substituted imidazotriazinones, processes for their preparation, and their use for the production of medicaments, in particular for improving **perception**, concentration power, **learning** power and/or **memory** power.

SUMM . . . to new substituted imidazotriazinones, processes for their preparation, and their use for the production of medicaments, in particular for improving **perception**, concentration power, **learning** power and/or **memory** power.

SUMM [0003] The particular feature of **PDE 2** lies in its positive cooperative kinetics with respect to the substrate cGMP. It was postulated that small amounts of cGMP. . . . the catalytic domain to cGMP and cAMP is also increased (Martins et al. J. Biol. Chem. 1982, 257, 1973-1979). Therefore **PDE 2** can hydrolyse and thereby also control both second messenger systems by means of small amounts of cGMP.

SUMM [0004] **PDE 2** has been isolated from various tissues, for example from heart, adrenal gland, liver, platelets and in particular brain. In the brain, **PDE 2** mRNA is expressed strongly in the cortex, the basal ganglia and in the hippocampus (Sonnenburg et al. Biol. Chem. 1991,. . .

SUMM [0095] The compounds according to the invention show an unforeseeable, valuable spectrum of pharmacological action: they preferably inhibit **PDE 2**, and/or exhibit a favourable pharmacokinetic profile.

SUMM [0096] The inhibition of **PDE 2** leads to a differentiated increase in cGMP. The differentiating action is additionally determined by the distribution of the isoenzymes in. . .

SUMM [0098] Because of their selective **PDE 2** inhibition, the compounds according to the invention are particularly suitable for improving **perception**, concentration power, **learning** power or **memory** power, in particular after **cognitive** disorders, such as occur, for example, in situations/illnesses/syndromes such as mild **cognitive** impairment, age-associated **learning** and **memory** disorders, age-associated **memory** losses, vascular **dementia**, craniocerebral trauma, stroke, **dementia** which occurs after strokes (post-stroke **dementia**), post-traumatic craniocerebral trauma, general concentration disorders, concentration disorders in children with **learning** and **memory** problems, **Alzheimer** 's disease, vascular **dementia**, **dementia** with Lewy bodies, **dementia** with degeneration of the frontal lobes including Pick's disease, Parkinson's disease, progressive nuclear palsy, **dementia** with corticobasal degeneration, amyolateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob **dementia**, HIV **dementia** , schizophrenia with **dementia** or Korsakoff psychosis.

SUMM [0099] The compounds according to the invention are generally suitable for the treatment and/or prophylaxis of **dementia**.

SUMM [0109] The cGMP-stimulable PDE (**PDE 2**), the cGMP-inhibitable PDE (PDE 3) and the cAMP-specific PDE (PDE 4) were isolated either from porcine or bovine heart myocardium.. . .

SUMM . . . about 50% of the substrate are reacted during the incubation time of 30 min. In order to test the cGMP-stimulable **PDE 2**, [.sup.3H]-cAMP is used as a substrate and 10.sup.-6 mol/l of non-labelled cGMP is added to the batch. In order to. . .

SUMM [0111] The activity of the test substances on **PDE 2** was determined using the [.sup.3H] cAMP Scintillation Proximity Assay (SPA) kit (TRKQ7090) from Amersham International (Little Chalfont, England) or on. . .

SUMM . . . this solution was further diluted with H.sub.2O (highest final concentration in the test: 10 .mu.M). For the prestimulation of the **PDE 2**, cGMP is additionally added (final concentration in the test: 10.sup.-6 M). The enzyme is diluted in PDE buffer (20 mM. . .

SUMM [0114] For example, under the conditions indicated above Example 2 inhibits the **PDE 2** with an IC.sub.50 value of 10 nM.

SUMM [0116] **PDE 2** inhibitors increase the intracellular neuronal cGMP concentration after prestimulation of the guanylate cyclase using 10.sup.-4 M sodium nitroprusside (SNP) in. . .

SUMM [0120] The object recognition test is a **memory** test. It measures the ability of rats (and mice) to differentiate between known and unknown objects and is therefore suitable for the determination of the **memory**-improving action of the compounds according to the invention.

SUMM . . . already examined in the first passage, and will therefore inspect both objects equally intensively. The administration of a substance having **learning**- and **memory**-improving action will lead to a rat recognizing the object already seen 24 hours beforehand, in the first passage, as known. It will examine the new, unknown object in greater detail than the already known one. This **memory** power is expressed in a discrimination index. A discrimination index of zero means that the rat examines both objects, the. . .

CLM What is claimed is:

9. Compounds according to one of claims 1 to 4 for improving **perception**, concentration power, **learning** power and/or **memory** power.

10. Compounds according to one of claims 1 to 4 for the treatment and/or prophylaxis of disorders of **perception**, concentration power, **learning** power and/or **memory** power.

. . . 11. Use of compounds according to one of claims 1 to 4 for the production of a medicament for improving **perception**, concentration power, **learning** power and/or **memory** power.

. . . one of claims 1 to 4 for the production of a medicament for the treatment and/or prophylaxis of disorders of **perception**, concentration power, **learning** power and/or **memory** power.

13. Use according to claim 12, the disorder being a result of **dementia**.

14. Use of compounds according to one of claims 1 to 4 for the production of a medicament for the treatment and/or prophylaxis of **dementia**.

L13 ANSWER 7 OF 106 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:98116 CAPLUS
DOCUMENT NUMBER: 94:98116
TITLE: Flow of information in the light-triggered cyclic nucleotide cascade of **vision**
AUTHOR(S): Fung, Bernard K. K.; Hurley, James B.; Stryer, Lubert
CORPORATE SOURCE: Sch. Med., Stanford Univ., Stanford, CA, 94305, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1981), 78(1), 152-6
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Photolyzed rhodopsin (I) catalyzes the exchange of GTP for GDP bound to a protein in retinal rod outer segments. It has been previously proposed that the GTP complex of this protein regulates cyclic GMP **phosphodiesterase** (**II**) and that it may be the 1st amplified intermediate in **visual** excitation. The identification and characterization of transducin (III), a regulatory protein consisting of 3 kinds of polypeptide chains, III.alpha. (39 kilodaltons), III.beta. (36 kilodaltons), and III.gamma. (.apprx.10 kilodaltons), is reported. Reconstituted membranes contg. I and III, but no II, exhibited GTPase activity and amplified the binding of guanosine 5'-(.beta.,.gamma.-imido)triphosphate (IV), a nonhydrolyzable analog of GTP, on illumination. A single photolyzed I mol. led to the uptake of IV by 71 mols. of III. High-pressure liq. chromatog. showed that the binding site for GTP is on the .alpha. subunit of III. II on unilluminated disk membranes could be fully activated by addn. of III.alpha. contg. bound IV. These findings strongly suggest that III is the 1st amplified information-carrying intermediate in the cyclic nucleotide cascade of **vision**.

TI Flow of information in the light-triggered cyclic nucleotide cascade of **vision**

AB Photolyzed rhodopsin (I) catalyzes the exchange of GTP for GDP bound to a protein in retinal rod outer segments. It has been previously proposed that the GTP complex of this protein regulates cyclic GMP **phosphodiesterase** (**II**) and that it may be the 1st amplified intermediate in **visual** excitation. The identification and characterization of transducin (III), a regulatory protein consisting of 3 kinds of polypeptide chains, III.alpha. (39 kilodaltons), III.beta. (36 kilodaltons), and III.gamma. (.apprx.10 kilodaltons), is reported. Reconstituted membranes contg. I and III, but no II, exhibited GTPase activity and amplified the binding of guanosine 5'-(.beta.,.gamma.-imido)triphosphate (IV), a nonhydrolyzable analog of GTP, on illumination. A single photolyzed I mol. led to the uptake of IV by 71 mols. of III. High-pressure liq. chromatog. showed that the binding site for GTP is on the .alpha. subunit of III. II on unilluminated disk membranes could be fully activated by addn. of III.alpha. contg. bound IV. These findings strongly suggest that III is the 1st amplified information-carrying intermediate in the cyclic nucleotide cascade of **vision**.

ST transducin **vision** excitation process mechanism; GTPase **vision** photoprocess transducin rhodopsin; cyclic GMP phosphodiesterase regulation transducin

IT Rhodopsins
RL: BIOL (Biological study)
(GTPase activity of reconstituted photomembrane contg. transducin and, **vision** primary excitation process in relation to)

IT Transducins
RL: BIOL (Biological study)
(as cyclic GMP phosphodiesterase regulatory protein, in **vision** primary excitation process)

IT Proteins
RL: BIOL (Biological study)
(cyclic GMP phosphodiesterase-regulating, transducin as, in **vision** primary excitation process)

IT Light, biological effects
(cyclic nucleotide cascade of **vision** triggered by, transducin role in)

IT **Vision**
(primary excitation process of, transducin role in)

IT Eye, composition
(rod outer segment, transducin in, **vision** primary excitation process in relation to)

IT 9059-32-9
RL: BIOL (Biological study)

(of reconstituted photomembrane contg. transducin and rhodopsin, **vision** primary excitation process in relation to)
IT 34273-04-6
RL: BIOL (Biological study)
(transducin binding of, in reconstituted photomembrane, **vision** cyclic nucleotide cascade in relation to)

L13 ANSWER 8 OF 106 USPATFULL
ACCESSION NUMBER: 2002:273438 USPATFULL
TITLE: Phosphodiesterase 4 inhibitors
INVENTOR(S): Schumacher, Richard A., Monroe, NY, UNITED STATES
Brubaker, William F., JR., Cheshire, CT, UNITED STATES
De Vivo, Michael, New York, NY, UNITED STATES
Hess, Hans-Jurgen Ernst, Old Lyme, CT, UNITED STATES
Hopper, Allen, Glen Rock, NJ, UNITED STATES
Tehim, Ashok, Ridgewood, NJ, UNITED STATES
Liu, Ruiping, Huntington, NY, UNITED STATES
Unterbeck, Axel, Madison, CT, UNITED STATES
PATENT ASSIGNEE(S): MEMORY PHARMACEUTICALS CORP., Montvale, NJ, UNITED STATES (U.S. corporation)

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 2002151566 | A1 | 20021017 | |
| APPLICATION INFO.: | US 2002-51309 | A1 | 20020122 | (10) |

| | NUMBER | DATE | |
|---|---|---|---|
| PRIORITY INFORMATION: | US 2001-306140P | 20010719 | (60) |
| | US 2000-257196P | 20001222 | (60) |
| | US 2001-262651P | 20010122 | (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201
NUMBER OF CLAIMS: 59
EXEMPLARY CLAIM: 1
LINE COUNT: 3689
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB PDE4 inhibition is achieved by novel compounds, e.g., N-substituted aniline and diphenylamine analogs. The compounds of the present invention are of Formula I: ##STR1##

wherein R.sup.1, R.sup.2 , R.sup.3and R.sup.4 are as defined herein.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . by calcium, calmodulin or cGMP, and their selective inhibition by various compounds. For example, PDE 1 is stimulated by Ca.sup.2+/calmodulin. **PDE 2** is cGMP-dependent, and is found in the heart and adrenals. PDE 3 is cGMP-dependent, and inhibition of this enzyme creates. . .
SUMM . . . catalyzing its hydrolysis to adenosine 5'-monophosphate (AMP). Regulation of cAMP activity is important in many biological processes, including inflammation and **memory**. Inhibitors of PDE4 isoenzymes such as rolipram, piclamilast, CDP-840 and ariflo are powerful antiinflammatory agents and therefore may be useful in treating diseases where inflammation is problematic such as asthma or arthritis. Further, rolipram improves the **cognitive** performance of rats and mice in **learning** paradigms. ##STR2##
SUMM . . . rolipram, xanthine derivatives such as pentoxifylline, denbufylline, and theophylline inhibit PDE4 and have received considerable attention of late for their **cognition** enhancing

effects. cAMP and cGMP are second messengers that mediate cellular responses to many different hormones and neurotransmitters. Thus, therapeutically. . .

SUMM . . . work in the PDE4 field focused on depression and inflammation, and has subsequently been extended to include indications such as **dementia**. [see "The PDE IV Family Of Calcium-Phosphodiesterases Enzymes," John A. Lowe, III, et al., Drugs of the Future 1992, 17(9):799-807. . .

SUMM . . . that involves elevated intracellular PDE 4 levels or decreased cAMP levels, e.g., involving neurological syndromes, especially those states associated with **memory** impairment, most especially long term **memory** impairment, as where such **memory** impairment is due in part to catabolism of intracellular cAMP levels by PDE4 enzymes, or where such **memory** impairment may be improved by effectively inhibiting PDE4 enzyme activity.

SUMM . . . the activity of PDE4 in animals, e.g., mammals, especially humans. These compounds exhibit neurological activity, especially where such activity affects **cognition**, including long term **memory**. These compounds will also be effective in treating diseases where decreased cAMP levels are involved. This includes but is not limited to inflammatory diseases. These compounds may also function as antidepressants, or be useful in treating **cognitive** and negative symptoms of schizophrenia.

SUMM . . . an animal model, or in a mammal or in a human); a method of treating neurological syndrome, e.g., loss of **memory**, especially long-term **memory**, **cognitive** impairment or decline, **memory** impairment, etc. a method of treating a disease state modulated by PDE4 activity, in a mammal, e.g., a human, e.g.,. . .

SUMM . . . inhibition, the compounds of the present invention can be administered to anyone requiring or desiring PDE4 inhibition, and/or enhancement of **cognition**. Administration may be accomplished according to patient needs, for example, orally, nasally, parenterally (subcutaneously, intraveneously, intramuscularly, intrastemally and by infusion),. . .

SUMM . . . the sole active agent or in combination with other pharmaceutical agents such as other agents used in the treatment of **cognitive** impairment and/or in the treatment of psychosis, e.g., other PDE4 inhibitors, calcium channel blockers, chloinergic drugs, adenosine receptor modulators, amphakines. . .

SUMM . . . has a therapeutic effect, such as where such inhibition may relieve conditions involving neurological syndromes, such as the loss of **memory**, especially long-term **memory**. Such methods comprise administering to an animal in need thereof, especially a mammal, most especially a human, an inhibitory amount. . .

SUMM [0190] The condition of **memory** impairment is manifested by impairment of the ability to **learn** new information and/or the inability to recall previously **learned** information. **Memory** impairment is a primary symptom of **dementia** and can also be a symptom associated with such diseases as **Alzheimer**'s disease, schizophrenia, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeld-Jakob disease, HIV, cardiovascular disease, and head trauma as well as age-related **cognitive** decline.

SUMM [0191] **Dementias** are diseases that include **memory** loss and additional intellectual impairment separate from **memory**. The present invention includes methods for treating patients suffering from **memory** impairment in all forms of **dementia**. **Dementias** are classified according to their cause and include: neurodegenerative **dementias** (e.g., **Alzheimer**'s, Parkinson's disease, Huntington's disease, Pick's disease), vascular (e.g., infarcts, hemorrhage, cardiac disorders), mixed vascular and **Alzheimer**'s, bacterial meningitis, Creutzfeld-Jacob Disease,

multiple sclerosis, traumatic (e.g., subdural hematoma or traumatic brain injury), infectious (e.g., HIV), genetic (down syndrome),. . .

SUMM [0192] The present invention includes methods for dealing with **memory** loss separate from **dementia**, including mild **cognitive** impairment (MCI) and age-related **cognitive** decline. The present invention includes methods of treatment for **memory** impairment as a result of disease. In another application, the invention includes methods for dealing with **memory** loss resulting from the use of general anesthetics, chemotherapy, radiation treatment, post-surgical trauma, and therapeutic intervention.

SUMM . . . properties make these compounds useful to treat neurodegeneration resulting from any disease or injury, including stroke, spinal cord injury, neurogenesis, **Alzheimer**'s disease, multiple sclerosis, amylolaterosclerosis (ALS), and multiple systems atrophy (MSA).

SUMM [0194] Thus, in accordance with a preferred embodiment, the present invention includes methods of treating patients suffering from **memory** impairment due to, for example, **Alzheimer**'s disease, schizophrenia, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeld-Jakob disease, depression, aging, head trauma, stroke, CNS hypoxia, cerebral senility, multiinfarct **dementia** and other neurological conditions including acute neuronal diseases, as well as HIV and cardiovascular diseases, comprising administering an effective amount. . .

SUMM . . . vascular ischemia-reperfusion injury (IRI), for corneal hydration, for inhibition of IL-2R expression and thereby abolishing HIV-1 DNA nuclear import into **memory** T cells, for augmentation of glucose-induced insulin secretion, in both the prevention and treatment of colitis, and to inhibit mast. . .

SUMM . . . the sole active agent or in combination with other pharmaceutical agents such as other agents used in the treatment of **cognitive** impairment and/or in the treatment of psychosis, e.g., other PDE4 inhibitors, calcium channel blockers, chloinergic drugs, adenosine receptor modulators, amphakines. . .

DETD Passive Avoidance in Rats, an in vivo Test for **Learning** and **Memory**

DETD Radial arm maze task in Rats, an in vivo Test for **Learning** and **Memory**

DETD . . . until it collected all pellets of food or 10 minutes passed, whichever came first. Four parameters were recorded: 1) working **memory** errors, i.e., entries into baited arms that had already been visited during the same trial; 2) reference **memory** errors, i.e., entries into unbaited arms; 3) total arm entries; and 4) the test duration (seconds), i.e., the time spent in the collection of all the pellets in the maze. If the working **memory** error was zero and the average reference **memory** error was less than one in five successive trials, the rats began the drug tests. MK-801 or saline was injected. . . agent, which was given 45 minutes before the test. Experiments were performed in a lighted room, which contained several extra-maze **visual** cues.

DETD . . . were made using Kewman-Keuls tests. Compared to control, MK-801 (0.1 mg/kg, i.p.) increased the frequencies of both working and reference **memory** errors ($p<0.01$). This amnesic effect of MK-801 on working **memory** is reversed in a statistically significant manner by the administration of actual test compounds in a dose-dependent fashion (e.g., 3-cyclopentyloxy-4-methoxy-N-(3-pyridylmethyl)diphenylamine,. . .

CLM What is claimed is:

42. A method for enhancing **cognition** in a patient in whom such enhancement is desired comprising administering to said patient an effective amount of a compound. . .

45. A method of treating a patient suffering from **cognition** impairment or decline comprising administering to said patient an effective amount of a compound according to claim 1.

47. A method according to claim 46, wherein said patient is suffering from **memory** impairment.

49. A method according to claim 47, wherein said patient is suffering from **memory** impairment due to **Alzheimer**'s disease, schizophrenia, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeld-Jakob disease, depression, aging, head trauma, stroke, CNS hypoxia, cerebral senility, multiinfarct **dementia**, HIV or cardiovascular disease.

54. A method of treating a patient suffering from **memory** impairment due to a ineurodegenerative disease comprising administering to said patient an effective amount of a compound according to claim. . .

55. A method of treating a patient suffering from **memory** impairment due to an acute neurodegenerative disorder comprising administering to said patient an effective amount of a compound according to. . .

L13 ANSWER 9 OF 106 USPATFULL

| | | | |
|---|---|---|---|
| ACCESSION NUMBER: | 2003:11102 USPATFULL | | |
| TITLE: | Therapeutic use of selective PDE10 inhibitors | | |
| INVENTOR(S): | Lebel, Lorraine A., North Stonington, CT, UNITED STATES<br>Menniti, Frank S., Mystic, CT, UNITED STATES<br>Schmidt, Christopher J., Old Lyme, CT, UNITED STATES | | |
| PATENT ASSIGNEE(S): | Pfizer Inc (U.S. corporation) | | |
| | NUMBER | KIND | DATE |
| PATENT INFORMATION: | US 2003008806 | A1 | 20030109 |
| APPLICATION INFO.: | US 2002-126113 | A1 | 20020419 (10) |
| | NUMBER | | DATE |
| PRIORITY INFORMATION: | US 2001-285148P | | 20010420 (60) |
| DOCUMENT TYPE: | Utility | | |
| FILE SEGMENT: | APPLICATION | | |
| LEGAL REPRESENTATIVE: | PFIZER INC, 150 EAST 42ND STREET, 5TH FLOOR - STOP 49, NEW YORK, NY, 10017-5612 | | |
| NUMBER OF CLAIMS: | 19 | | |
| EXEMPLARY CLAIM: | 1 | | |
| NUMBER OF DRAWINGS: | 2 Drawing Page(s) | | |
| LINE COUNT: | 861 | | |

AB The invention provides a method for treating certain neurologic and psychiatric disorders in mammals, including humans, comprising administration of a selective PDE10 inhbitor. In particular, the invention relates to treatment of mood, movement, and anxiety disorders; psychosis; drug, for example alcohol, addiction; and disorders having as a symptom deficient **cognition**. The invention furthermore provides the use of papaverine as a selective inhibitor of PDE10.

AB . . . treatment of mood, movement, and anxiety disorders; psychosis; drug, for example alcohol, addiction; and disorders having as a symptom deficient **cognition**. The invention furthermore provides the use of papaverine as a selective inhibitor of PDE10.

SUMM . . . system. More particularly, the invention relates to treatment of neurologic and psychiatric disorders, for example psychosis and disorders comprising deficient **cognition** as a symptom. This

invention also relates to PDE10 inhibition.

SUMM [0019] This invention further provides a method of treating a disorder comprising as a symptom a deficiency in **cognition** in a mammal, including a human, which method comprises administering to said mammal an amount of a selective PDE10 inhibitor effective in treating a deficiency **cognition**.

SUMM [0020] This invention also provides a method of treating a disorder comprising as a symptom a deficiency in **cognition** in a mammal, including a human, which method comprises administering to said mammal an amount of a selective PDE10 inhibitor. . .

SUMM [0021] The phrase "deficiency in **cognition**" as used herein in "disorder comprising as a symptom a deficiency in **cognition**" refers to a subnormal functioning in one or more **cognitive** aspects such as **memory**, intellect, or **learning** and logic ability, in a particular individual relative to other individuals within the same general age population. "Deficiency in **cognition** " also refers to a reduction in any particular individual's functioning in one or more **cognitive** aspects, for example as occurs in age-related **cognitive** decline.

SUMM [0022] Examples of disorders that comprise as a symptom a deficiency in **cognition** that can be treated according to the present invention are **dementia**, for example **Alzheimer**'s disease, multi-infarct **dementia**, alcoholic **dementia** or other drug-related **dementia**, **dementia** associated with intracranial tumors or cerebral trauma, **dementia** associated with Huntington's disease or Parkinson's disease, or AIDS-related **dementia**; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a **learning** disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; and age-related **cognitive** decline.

SUMM . . . example treating, delusions and/or hallucination associated therewith. Other examples of symptoms of schizophrenia and schizophreniform and schizoaffecctive disorders include disorganized **speech**, affective flattening, alogia, anhedonia, inappropriate affect, dysphoric mood (in the form of, for example, depression, anxiety or anger), and some indications of **cognitive** dysfunction.

DETD [0037] **PDEs 2**, 3 and 5, isozymes, including human PDEs, can, for example, be prepared from corpus cavernosum; PDE1, isozymes including human, from. . .

DETD [0053] Studies in human and non-human mammals indicate that the basal ganglia regulate a range of motor as well as **cognition** and emotional/appetitive behaviors (Graybiel, A. M. Current Biology 10 (14):R509-11, 2000). Experimental models in rodents have been developed which can. . .

DETD . . . antipsychotic agents. More recently, the ability of NMDA receptor antagonist such as PCP to faithfully reproduced the positive, negative and **cognitive** symptoms of schizophrenia in man (Luby et al., 1959; Rosenbaum et al., 1959; Krystal et al. 1994) has lead to. . .

DETD . . . As disclosed above, we have found PDE10 mRNA and protein expressed also in neurons of the hippocampus and cortex. Since **cognitive** processes are dependant on hippocampus and cortex functioning, we believe that PDE10 also plays a role in **cognitive** processes and that a PDE10 inhibitor may be used to treat disorders having a characteristic component of deficient **cognitive** function, such as **Alzheimer**'s disease and age-related **cognitive** decline (ARCD).

CLM What is claimed is:

6. A method of treating a disorder comprising as a symptom a deficiency in **cognition** in a mammal, which method comprises administering to said mammal an amount of a selective PDE10 inhibitor effective in

treating deficient **cognition**.

7. A method according to claim 6, wherein the disorder is selected from **dementia**, for example **Alzheimer**'s disease, multi-infarct **dementia**, alcoholic **dementia** or other drug-related **dementia**, **dementia** associated with intracranial tumors or cerebral trauma, **dementia** associated with Huntington's disease or Parkinson's disease, or AIDS-related **dementia**; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a **learning** disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; and age-related **cognitive** decline.

16. A method of treating a disorder comprising as a symptom a deficiency in **cognition** in a mammal, which method comprises administering to said mammal an amount of a selective PDE10 inhibitor effective in inhibiting. . .
17. A method according to claim 16, wherein the disorder is selected from **dementia**, for example **Alzheimer**'s disease, multi-infarct **dementia**, alcoholic **dementia** or other drug-related **dementia**, **dementia** associated with intracranial tumors or cerebral trauma, **dementia** associated with Huntington's disease or Parkinson's disease, or AIDS-related **dementia**; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a **learning** disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; and age-related **cognitive** decline.

L13 ANSWER 10 OF 106 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:504946 CAPLUS
DOCUMENT NUMBER: 136:165258
TITLE: Decreased brain levels of 2',3'-cyclic nucleotide-3'-phosphodiesterase in Down syndrome and **Alzheimer**'s disease
AUTHOR(S): Vlkolinsky, R.; Cairns, N.; Fountoulakis, M.; Lubec, G.
CORPORATE SOURCE: Department of Pediatrics, University of Vienna, Vienna, 1090, Austria
SOURCE: Neurobiology of Aging (2001), 22(4), 547-553
CODEN: NEAGDO; ISSN: 0197-4580
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In Down syndrome (DS) as well as in **Alzheimer**'s disease (AD) oligodendroglial and myelin alterations have been reported. 2',3'-cyclic nucleotide-3'-phosphodiesterase (CNPase) and carbonic anhydrase II (CA II) are widely accepted as markers for oligodendroglia and myelin. However, only data on CNPase activity have been available in AD and DS brains so far. In our study we detd. the protein levels of CNPase and CA II in DS, AD and in control post mortem brain samples in order to assess oligodendroglia and myelin alterations in both diseases. We used two dimensional electrophoresis to sep. brain proteins that were subsequently identified by matrix assisted laser desorption and ionization mass-spectroscopy (MALDI-MS). Seven brain areas were investigated (frontal, temporal, occipital and parietal cortex, cerebellum, thalamus and caudate nucleus). In comparison to control brains we detected significantly decreased CNPase protein levels in frontal and temporal cortex of DS patients. The level of CA II protein in DS was unchanged in comparison to controls. In AD brains levels of CNPase were decreased in

frontal cortex only. The level of CA II in all brain areas in AD group was comparable to controls. Changes of CNPase protein levels in DS and AD are in agreement with the previous finding of decreased CNPase activity in DS and AD brain. They probably reflect decreased oligodendroglial d. and/or reduced myelination. These can be secondary to disturbances in axon/oligodendroglial communication due to neuronal loss present in both diseases. Alternatively, reduced CNPase levels in DS brains may be caused by impairment of glucose metab. and/or alterations of thyroid functions.

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Decreased brain levels of 2',3'-cyclic nucleotide-3'-phosphodiesterase in Down syndrome and **Alzheimer**'s disease

AB In Down syndrome (DS) as well as in **Alzheimer**'s disease (AD) oligodendroglial and myelin alterations have been reported. 2',3'-cyclic nucleotide-3'-phosphodiesterase (CNPase) and carbonic anhydrase II (CA II) are widely accepted as markers for oligodendroglia and myelin. However, only data on CNPase activity have been available in AD and DS brains so far. In our study we detd. the protein levels of CNPase and CA II in DS, AD and in control post mortem brain samples in order to assess oligodendroglia and myelin alterations in both diseases. We used two dimensional electrophoresis to sep. brain proteins that were subsequently identified by matrix assisted laser desorption and ionization mass-spectroscopy (MALDI-MS). Seven brain areas were investigated (frontal, temporal, occipital and parietal cortex, cerebellum, thalamus and caudate nucleus). In comparison to control brains we detected significantly decreased CNPase protein levels in frontal and temporal cortex of DS patients. The level of CA II protein in DS was unchanged in comparison to controls. In AD brains levels of CNPase were decreased in frontal cortex only. The level of CA II in all brain areas in AD group was comparable to controls. Changes of CNPase protein levels in DS and AD are in agreement with the previous finding of decreased CNPase activity in DS and AD brain. They probably reflect decreased oligodendroglial d. and/or reduced myelination. These can be secondary to disturbances in axon/oligodendroglial communication due to neuronal loss present in both diseases. Alternatively, reduced CNPase levels in DS brains may be caused by impairment of glucose metab. and/or alterations of thyroid functions.

ST cyclic nucleotide phosphodiesterase carbonic anhydrase Down syndrome **Alzheimers** disease

IT **Alzheimer**'s disease
Biomarkers (biological responses)
Down's syndrome
Human
Oligodendrocyte
(2',3'-cyclic nucleotide-3'-phosphodiesterase and carbonic anhydrase II in brain regions in Down syndrome and **Alzheimer**'s disease)

IT Myelin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(2',3'-cyclic nucleotide-3'-phosphodiesterase and carbonic anhydrase II in brain regions in Down syndrome and **Alzheimer**'s disease)

IT Brain
(caudate nucleus; 2',3'-cyclic nucleotide-3'-phosphodiesterase and carbonic anhydrase II in brain regions in Down syndrome and **Alzheimer**'s disease)

IT Brain
(cerebellum; 2',3'-cyclic nucleotide-3'-phosphodiesterase and carbonic anhydrase II in brain regions in Down syndrome and **Alzheimer**'s disease)

IT Brain
(frontal cortex; 2',3'-cyclic nucleotide-3'-phosphodiesterase and carbonic anhydrase II in brain regions in Down syndrome and **Alzheimer**'s disease)

IT Brain

(occipital cortex; 2',3'-cyclic nucleotide-3'-phosphodiesterase and carbonic anhydrase II in brain regions in Down syndrome and **Alzheimer**'s disease)
IT Brain
(parietal cortex; 2',3'-cyclic nucleotide-3'-phosphodiesterase and carbonic anhydrase II in brain regions in Down syndrome and **Alzheimer**'s disease)
IT Brain
(temporal cortex; 2',3'-cyclic nucleotide-3'-phosphodiesterase and carbonic anhydrase II in brain regions in Down syndrome and **Alzheimer**'s disease)
IT Brain
(thalamus; 2',3'-cyclic nucleotide-3'-phosphodiesterase and carbonic anhydrase II in brain regions in Down syndrome and **Alzheimer**'s disease)
IT 60098-35-3, 2',3'-Cyclic nucleotide-3'-**phosphodiesterase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**2**',3'-cyclic nucleotide-3'-phosphodiesterase and carbonic anhydrase II in brain regions in Down syndrome and **Alzheimer**'s disease)
IT 9001-03-0
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(II; 2',3'-cyclic nucleotide-3'-phosphodiesterase and carbonic anhydrase II in brain regions in Down syndrome and **Alzheimer**'s disease)

=> d ibib abs kwic 11-15

L13 ANSWER 11 OF 106 MEDLINE
ACCESSION NUMBER: 83163353 MEDLINE
DOCUMENT NUMBER: 83163353 PubMed ID: 6300356
TITLE: Cyclic adenosine 3':5'-monophosphate phosphodiesterase and its role in **learning** in Drosophila.
AUTHOR: Shotwell S L
CONTRACT NUMBER: GM-07616 (NIGMS)
SOURCE: JOURNAL OF NEUROSCIENCE, (1983 Apr) 3 (4) 739-47.
Journal code: 8102140. ISSN: 0270-6474.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198305
ENTRY DATE: Entered STN: 19900318
Last Updated on STN: 19970203
Entered Medline: 19830527

AB Drosophila carrying the X-linked mutation dunce (dnc) showed poor **learning** in a negative reinforcement olfactory conditioning paradigm (Dudai, Y., Y.-N. Jan, D. Byers, W.G. Quinn, and S. Benzer (1976) Proc. Natl. Acad. Sci. U.S.A. 73: 1684-1688). More recently, dnc flies were shown to have reduced activity for one of two cAMP phosphodiesterases (PDEs) present in normal flies, **PDE II**, whereas PDE form I was unaffected (Byers, D., R. L. Davis, and J. A. Kiger, Jr. (1981) Nature 289: 79-81). A micro-assay technique is described that allows the separate measurement of PDE I and **PDE II** in crude extracts, based on specific inhibition of PDE I [3H]cAMP hydrolysis by cGMP. Using this technique, **PDE II** is shown to occur normally at high specific activity in the nervous system, consistent with the hypothesis that this enzyme plays a role in neuronal function. Reduced **PDE II** activity correlates with poor **learning** in dnc flies at three developmental stages (first and third instar larva and adult), as well as in response to genetic modification of dnc gene

activity. Biochemical and genetic experiments fail to reveal any abnormal regulation of **PDE II** in dnc. The specific activity of **PDE II** is shown to correlate in a one to one fashion with the level of normal dnc gene (dnc+) activity at five different doses of dnc+. These results support the hypothesis that **PDE II** represents the primary product of the dnc gene, indicating a role for this enzyme in Drosophila **learning**.

TI Cyclic adenosine 3':5'-monophosphate phosphodiesterase and its role in **learning** in Drosophila.

AB Drosophila carrying the X-linked mutation dunce (dnc) showed poor **learning** in a negative reinforcement olfactory conditioning paradigm (Dudai, Y., Y.-N. Jan, D. Byers, W.G. Quinn, and S. Benzer (1976) Proc.. . . recently, dnc flies were shown to have reduced activity for one of two cAMP phosphodiesterases (PDEs) present in normal flies, **PDE II**, whereas PDE form I was unaffected (Byers, D., R. L. Davis, and J. A. Kiger, Jr. (1981) Nature 289: 79-81). A micro-assay technique is described that allows the separate measurement of PDE I and **PDE II** in crude extracts, based on specific inhibition of PDE I [3H]cAMP hydrolysis by cGMP. Using this technique, **PDE II** is shown to occur normally at high specific activity in the nervous system, consistent with the hypothesis that this enzyme plays a role in neuronal function. Reduced **PDE II** activity correlates with poor **learning** in dnc flies at three developmental stages (first and third instar larva and adult), as well as in response to genetic modification of dnc gene activity. Biochemical and genetic experiments fail to reveal any abnormal regulation of **PDE II** in dnc. The specific activity of **PDE II** is shown to correlate in a one to one fashion with the level of normal dnc gene (dnc+) activity at five different doses of dnc+. These results support the hypothesis that **PDE II** represents the primary product of the dnc gene, indicating a role for this enzyme in Drosophila **learning**.

CT . . . Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
*3',5'-Cyclic-Nucleotide Phosphodiesterase: ME, metabolism
Drosophila melanogaster: GE, genetics
*Drosophila melanogaster: PH, physiology
Genotype
Kinetics
***Learning**
Mutation
Organ Specificity
Sex Factors
X Chromosome

L13 ANSWER 12 OF 106 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:493350 CAPLUS
DOCUMENT NUMBER: 113:93350
TITLE: On **memory**, morphogenesis and the hormonal control of transcription
AUTHOR(S): Schiffmann, Yoram
CORPORATE SOURCE: Dep. Appl. Math. Theor. Phys., Univ. Cambridge, Cambridge, CB3 9EW, UK
SOURCE: Biochemical Society Transactions (1990), 18(4), 572-3
CODEN: BCSTB5; ISSN: 0300-5127
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 21 refs., on metabolic pathways. (1) Substrate inhibition autocatalysis involving cAMP, ATP, cAMP, adenylate cyclase, and cAMP **phosphodiesterase**, (2) lysogeny and homoeotic selector gene transcription, (3) glycogen breakdown and the Krebs cycle, and (4) the phospholipase C pathway are included.

TI On **memory**, morphogenesis and the hormonal control of

transcription
AB A review, with 21 refs., on metabolic pathways. (1) Substrate inhibition autocatalysis involving cAMP, ATP, cAMP, adenylate cyclase, and cAMP **phosphodiesterase**, (**2**) lysogeny and homoeotic selector gene transcription, (3) glycogen breakdown and the Krebs cycle, and (4) the phospholipase C pathway are included.
IT Hormones
RL: BIOL (Biological study)
(DNA transcription regulation by, **memory** and morphogenesis in relation to)
IT Ribonucleic acid formation
(regulation of, by hormones, **memory** and morphogenesis in relation to)
IT Deoxyribonucleic acids
RL: BIOL (Biological study)
(transcription of, hormones regulation of, **memory** and morphogenesis in relation to)

L13 ANSWER 13 OF 106 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1986:32634 CAPLUS
DOCUMENT NUMBER: 104:32634
TITLE: Phosphodiesterase-probes show distinct defects in rd mice and Irish setter dog disorders
AUTHOR(S): Lee, Rehwa H.; Lieberman, Bernice S.; Hurwitz, Richard L.; Lolley, Richard N.
CORPORATE SOURCE: Sch. Med., Univ. California, Los Angeles, CA, USA
SOURCE: Investigative Ophthalmology & Visual Science (1985), 26(11), 1569-79
CODEN: IOVSDA; ISSN: 0146-0404
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cGMP phosphodiesterase from the **visual** cells of rd mice and affected Irish setter dogs was analyzed, using biochem., biophys., and immunol. techniques. The mechanisms that cause a deficiency in phosphodiesterase activity in rd mice and Irish setter dogs are distinctly different. Apparently, the phosphodiesterase complex is normal in affected Irish setter dogs but is abnormal in rd mice. The criteria used for detg. the normalcy of the phosphodiesterase complex were sedimentation characteristics, immuno-crossreactivity, and histone-activation, which is a unique characteristic of the **visual** cell enzyme. According to these criteria, the phosphodiesterase complex in the **visual** cells of rd mice is either absent or abnormal from the onset of **visual** cell differentiation until degeneration, because (1) it exhibits no cross-reactivity with antibody to **phosphodiesterase**; (**2**) it is not activated by histone; and (3), if present, it exhibits abnormal sedimentation characteristics and perhaps subunit structure. Phosphodiesterase from the **visual** cells of affected Irish setter dogs is normal by the same criteria, because (1) it cross-reacts with antibody against **phosphodiesterase**; (**2**) it is activated by histone; and (3) it exhibits normal sedimentation and electrophoretic patterns. Depressed levels of phosphodiesterase activity in affected setter photoreceptors are due, perhaps, to a defect in the light-initiated cascade which activates the enzyme normally, in situ.
AB The cGMP phosphodiesterase from the **visual** cells of rd mice and affected Irish setter dogs was analyzed, using biochem., biophys., and immunol. techniques. The mechanisms that cause a deficiency in phosphodiesterase activity in rd mice and Irish setter dogs are distinctly different. Apparently, the phosphodiesterase complex is normal in affected Irish setter dogs but is abnormal in rd mice. The criteria used for detg. the normalcy of the phosphodiesterase complex were sedimentation characteristics, immuno-crossreactivity, and histone-activation, which is a unique characteristic of the **visual** cell enzyme. According to

these criteria, the phosphodiesterase complex in the **visual** cells of rd mice is either absent or abnormal from the onset of **visual** cell differentiation until degeneration, because (1) it exhibits no cross-reactivity with antibody to **phosphodiesterase**; (**2**) it is not activated by histone; and (3), if present, it exhibits abnormal sedimentation characteristics and perhaps subunit structure. Phosphodiesterase from the **visual** cells of affected Irish setter dogs is normal by the same criteria, because (1) it cross-reacts with antibody against **phosphodiesterase**; (**2** ) it is activated by histone; and (3) it exhibits normal sedimentation and electrophoretic patterns. Depressed levels of phosphodiesterase activity in affected setter photoreceptors are due, perhaps, to a defect in the light-initiated cascade which activates the enzyme normally, in situ.

L13 ANSWER 14 OF 106 MEDLINE
ACCESSION NUMBER: 83009254 MEDLINE
DOCUMENT NUMBER: 83009254 PubMed ID: 6288893
TITLE: Defective cyclic adenosine 3':5'-monophosphate phosphodiesterase in the Drosophila **memory** mutant dunce.
AUTHOR: Kauvar L M
SOURCE: JOURNAL OF NEUROSCIENCE, (1982 Oct) 2 (10) 1347-58. Journal code: 8102140. ISSN: 0270-6474.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198212
ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 19970203
Entered Medline: 19821203

AB A detailed characterization of the cyclic nucleotide phosphodiesterase (PDEs) from normal Drosophila melanogaster was made, including purification of the two major enzymes to near homogeneity. A third more labile phosphodiesterase also was identified in crude homogenates. The total activity per fly of one of these three enzymes, **PDE-II**, is strongly influenced by the dunce locus. Two independently derived dunce mutants produce variations of **PDE-II** with modified intrinsic properties: a marked decrease of thermal stability in dunce and a 10-fold increase in the Michaelis kinetic constant in dunce. These defects, which persisted in purified preparations of **PDE-II**, were mapped genetically to dunce. The results support the identification of dunce as the structural locus for **PDE-II**. The tight connection between the dunce gene and the **PDE-II** enzyme indicates that defective cyclic adenosine 3':5'-monophosphate metabolism is the primary lesion which leads to failure of dunce flies to **learn** in the olfactory associative conditioning paradigm of Quinn et al. (Quinn, W. G., W. A. Harris, and S. Benzer (1974) Proct. Natl. Acad. Sci. U. S. A. 71: 708-712).

TI Defective cyclic adenosine 3':5'-monophosphate phosphodiesterase in the Drosophila **memory** mutant dunce.

AB . . . more labile phosphodiesterase also was identified in crude homogenates. The total activity per fly of one of these three enzymes, **PDE-II**, is strongly influenced by the dunce locus. Two independently derived dunce mutants produce variations of **PDE-II** with modified intrinsic properties: a marked decrease of thermal stability in dunce and a 10-fold increase in the Michaelis kinetic constant in dunce. These defects, which persisted in purified preparations of **PDE-II**, were mapped genetically to dunce. The results support the identification of dunce as the structural locus for **PDE-II**. The tight connection between the dunce gene and the **PDE-II** enzyme indicates that defective cyclic

adenosine 3':5'-monophosphate metabolism is the primary lesion which leads to failure of dunce flies to **learn** in the olfactory associative conditioning paradigm of Quinn et al. (Quinn, W. G., W. A. Harris, and S. Benzer (1974). . .

CT . . .

Phosphodiesterase: GE, genetics
3',5'-Cyclic-Nucleotide Phosphodiesterase: IP, isolation & purification
Drosophila melanogaster: EN, enzymology
*Drosophila melanogaster: GE, genetics
Genes, Structural
Kinetics
***Learning**
*Mutation
Variation (Genetics)

L13 ANSWER 15 OF 106 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:36876 CAPLUS
DOCUMENT NUMBER: 110:36876
TITLE: cAMP-phosphodiesterase in the synaptic regions of Drosophila brain
AUTHOR(S): Devay, P.; Friedrich, P.
CORPORATE SOURCE: Inst. Enzymol., Hung. Acad. Sci., Budapest, H-1502, Hung.
SOURCE: Neuroscience Research Communications (1988), 3(2), 99-105
CODEN: NRCOEE; ISSN: 0893-6609
DOCUMENT TYPE: Journal
LANGUAGE: English

AB CAMP-phosphodiesterase (PDE) activity has been studied in the brain of wild-type and dunce-M11 **memory**-mutant D. melanogaster by electron microscopic histochem. In the wild-type fly, activity staining localized the enzyme in the synaptic region, whereas no activity was found in the same region of dunce-M11. PDE assays in vitro demonstrated that fixation damaged **PDE-II** less than PDE-I and suggested the existence of a cGMP-PDE activity distinct from PDE-I. It is concluded that the activity seen in the neuropil of wild-type brain stems from **PDE-II**.

AB CAMP-phosphodiesterase (PDE) activity has been studied in the brain of wild-type and dunce-M11 **memory**-mutant D. melanogaster by electron microscopic histochem. In the wild-type fly, activity staining localized the enzyme in the synaptic region, whereas no activity was found in the same region of dunce-M11. PDE assays in vitro demonstrated that fixation damaged **PDE-II** less than PDE-I and suggested the existence of a cGMP-PDE activity distinct from PDE-I. It is concluded that the activity seen in the neuropil of wild-type brain stems from **PDE-II**.

=> d ibib abs kwic 16-20

L13 ANSWER 16 OF 106 USPATFULL
ACCESSION NUMBER: 2002:268781 USPATFULL
TITLE: Methods for treatment of cystic fibrosis
INVENTOR(S): Earle, Keith A., North Wales, PA, United States
Alila, Hector W., North Wales, PA, United States
Whitehead, Clark M., Warminster, PA, United States
Thompson, W. Joseph, Doylestown, PA, United States
PATENT ASSIGNEE(S): Cell Pathways, Inc., Horsham, PA, United States (U.S. corporation)

| NUMBER | KIND | DATE |
|---|---|---|

PATENT INFORMATION: US 6465494 B1 20021015
APPLICATION INFO.: US 2001-938786 20010824 (9)
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Dees, Jose' G.
ASSISTANT EXAMINER: Gollamudi, Sharmila S
LEGAL REPRESENTATIVE: Stevenson, Robert W.
NUMBER OF CLAIMS: 37
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 16 Drawing Figure(s); 14 Drawing Page(s)
LINE COUNT: 1944
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Substituted condensation products of N-benzyl-3-indenylacetamides with heterocyclic aldehydes and other such inhibitors are useful for the treatment of cystic fibrosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . patients without the substantial side effects of prior pharmaceutical approaches. Specifically, this invention involves the administration of an inhibitor of **phosphodiesterase 2** ("PDE2") that also preferably inhibits phosphodiesterase 5 ("PDE5") to a mammal in need of treatment for cystic fibrosis. In narrower. . .

DRWD FIG. 13 is a **visual** image of immunostaining revealing the expression of **PDE-2** protein in macrophages in the lung of a 39-year old male patient with a known history of cystic fibrosis (60.times.).

DRWD FIG. 14 is a **visual** image of immunostaining revealing the expression of PDE-5 protein in alveolar macrophages in the lung of a 39-year old male. . .

DRWD FIG. 15 is a **visual** image of immunostaining revealing the expression of **PDE-2** protein in type II pneumocytes (pulmonary epithelial cells) in the lung of a 39-year old male patient with a known. . .

DRWD FIG. 16 is a **visual** image of immunostaining revealing the expression of PDE-5 protein in type II pneumocytes (pulmonary epithelial cells) in the lung of. . .

DETD . . . but different chemically. For example, software such as that sold by Molecular Simulations Inc. release of WebLab.RTM. ViewerPro.TM. includes molecular **visualization** and chemical communication capabilities. Such software includes functionality, including 3D **visualization** of known active compounds to validate sketched or imported chemical structures for accuracy. In addition, the software allows structures to. . .

DETD . . . sectioned at a thickness of 5 .mu.m. A serial dilution study demonstrated the optimal signal-to-noise ratio was 1:100 and 1:200 ( **PDE-2**), 1:500 and 1:1000 (PDE-5). Anti-**PDE-2** and anti-PDE-5 was used as the primary antibodies, and the principal detection system consisted of a Vector anti-sheep secondary (BA-6000). . .

DETD Human lung tissue samples exhibited positive staining for **PDE-2** and PDE-5 proteins and immunostaining was mostly localized to alveolar and pigment-laden macrophages. FIGS. 13 and 14 are **visual** images of immunostaining to **PDE-2** and PDE-5 proteins, respectively.

CLM What is claimed is:

. . . fibrosis in a mammal with that disease comprising administering to the mammal a physiologically effective amount of an inhibitor of **phosphodiesterase 2**(PDE2) wherein said inhibitor does not substantially inhibit cyclooxygenase I(COX I) or cyclooxygenase(COX) II.

L13 ANSWER 17 OF 106 USPATFULL
ACCESSION NUMBER: 95:36408 USPATFULL
TITLE: Xanthine derivatives
INVENTOR(S): Smith, David G., SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epson, Surrey, England
Buckle, Derek R., SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epson, Surrey, England
Fenwick, Ashley E., SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epson, Surrey, England KT18 5XQ

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 5409934 | | 19950425 | |
| | WO 9211260 | | 19920709 | |
| APPLICATION INFO.: | US 1993-78152 | | 19930707 | (8) |
| | WO 1991-GB2286 | | 19911219 | |
| | | | 19930707 | PCT 371 date |
| | | | 19930707 | PCT 102(e) date |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | GB 1990-27752 | 19901221 |
| | GB 1990-27899 | 19901221 |

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Berch, Mark L.
LEGAL REPRESENTATIVE: Kanagy, James, Suter, Stuart, Lentz, Edward
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
LINE COUNT: 1348
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . following transient forebrain ischaemia and are therefore useful in the treatment of cerebral vascular and neuronal degenerative disorders associated with **learning**, **memory** and **cognitive** dysfunctions including cerebral senility, multi-infarct **dementia**, senile **dementia** of the **Alzheimer** type, age associated **memory** impairment and certain disorders associated with Parkinson's disease.
SUMM . . . acceptable solvate thereof, for use in the treatments mentioned hereinbefore, such as cerebral vascular and neuronal denerative disorders associated with **learning**, **memory** and **cognitive** dysfunctions, peripheral vascular disease or proliferate skin disease or for the prophylaxis of disorders associated with neuronal degeneration resulting from. . .
DETD . . . showing stimulation of PDE activity by CA.sup.2+ and calmodulin were pooled and further purified on a calmodulin-affinity column. CGMP-stimulated PDE (**PDE II**), cG1VrP-inhibited PDE (PDE III) and cAMP-specific PDE (PDE IV) were all isolated from geinea-pig cardiac ventricle. Initial chromatography on a 20 ml Mono Q column resolved PDE III from a peak that contained both **PDE II** and PDE IV. The latter were separated by a cGMP-affinity column. The resolved PDEs were separately rechromatographed on a 1. . .
DETD With the exception of **PDE II**, which displayed positive cooperativity, all the preparations showed simple Michaelis-Menton kinetics (see Table 1 ).
DETD **PDE II** The activity of this isoenzyme with cAMP as a substrate was stimulated by cGMP. The isoenzyme could hydrolyse both

cAMP. . .
DETD . . . of the isoenzyme using 1 mM cAMP as a substrate for PDE I (in the absence of Ca.sup.2+ and calmodulin), **PDE II** and PDE V and with 1 mM cAMP as a substrate for PDE III and PDE IV.

L13 ANSWER 18 OF 106 USPATFULL
ACCESSION NUMBER: 2002:251792 USPATFULL
TITLE: New hydroxyindoles, their use as inhibitors of phosphodiesterase 4 and processes for their preparation
INVENTOR(S): Hofgen, Norbert, Ottendorf-Okrilla, GERMANY, FEDERAL REPUBLIC OF
Egerland, Ute, Radebeul, GERMANY, FEDERAL REPUBLIC OF
Poppe, Hildegard, Dresden, GERMANY, FEDERAL REPUBLIC OF
Marx, Degenhard, Radebeul, GERMANY, FEDERAL REPUBLIC OF
Szelenyi, Stefan, Schwaig, GERMANY, FEDERAL REPUBLIC OF
Kronbach, Thomas, Radebeul, GERMANY, FEDERAL REPUBLIC OF
Polymeropoulos, Emmanuel, Frankfurt, GERMANY, FEDERAL REPUBLIC OF
Heer, Sabine, Radebaul, GERMANY, FEDERAL REPUBLIC OF

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2002137745 | A1 | 20020926 |
| APPLICATION INFO.: | US 2002-81807 | A1 | 20020221 (10) |

RELATED APPLN. INFO.: Division of Ser. No. US 2000-653685, filed on 1 Sep 2000, ABANDONED Division of Ser. No. US 1999-300973, filed on 28 Apr 1999, GRANTED, Pat. No. US 6251923

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | DE 1998-19818964 | 19980428 |
| | DE 1999-19917504 | 19990417 |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FULBRIGHT & JAWORSKI, LLP, 666 FIFTH AVE, NEW YORK, NY, 10103-3198
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 1193
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to new hydroxyindoles of the Formula, ##STR1##

their use as inhibitors of phosphodiesterase 4 and processes for their preparation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . and can be used for the therapy of diseases in which neuroprotection is beneficial. Such disorders are, for example, senile **dementia** (**Alzheimer**'s disease), loss of **memory** , Parkinson's disease, depression, stroke and intermittent claudication.
DETD [0093] The PDE 4 inhibiting activity is determined in enzyme preparations of human polymorphonuclear lymphocytes (PMNLs), the **PDE 2**, 3 and 5 activity with PDE from human platelets. Human blood was anticoagulated with citrate. The thrombocyte-rich plasma in the. . . platelets are lysed by ultrasound and employed in the PDE 3 and PDE 5 assay. For the determination of the **PDE 2** activity, the cytosolic platelet fraction is purified on an anion exchange column by means of NaCl gradients and the **PDE 2** peak is recovered for the assay. The PMNLs for the PDE 4 determination are isolated by a following dextran sedimentation. . .
DETD . . . of the PDE 3 assay contain 10 .mu.M rolipram in order to

inhibit possible contamination by the PDE 4. The **PDE 2** is tested using an SPA assay from Amersham. The assay is carried out in the presence of the activator of **PDE 2** (5 .mu.M cGMP).

CLM What is claimed is:

. . . pneumonia, pulmonary infiltration with eosinophilia, urticaria, ulcerative colitis, Crohn's disease, psoriasis, keratosis, pulmonary neutrophilic infiltration, chronic obstructive pulmonary disease, senile **dementia**, loss of **memory**, Parkinson's disease, depression, stroke, intermittent claudication, benign prostate hyperplasia, pollakuria, nycturia, bladder atony, kidney stone colics, and analgesic dependency, which. . .

L13 ANSWER 19 OF 106 USPATFULL

ACCESSION NUMBER: 2002:221828 USPATFULL

TITLE: Hydroxyindoles, their use as inhibitors of phosphodiesterase 4 and processes for their preparation

INVENTOR(S): Hofgen, Norbert, Ottendorf-Okrilla, GERMANY, FEDERAL REPUBLIC OF
Egerland, Ute, Radebeul, GERMANY, FEDERAL REPUBLIC OF
Poppe, Hildegard, Dresden, GERMANY, FEDERAL REPUBLIC OF
Marx, Degenhard, Radebeul, GERMANY, FEDERAL REPUBLIC OF
Szelenyi, Stefan, Schwaig, GERMANY, FEDERAL REPUBLIC OF
Kronbach, Thomas, Radebeul, GERMANY, FEDERAL REPUBLIC OF
Polymeropoulos, Emmanuel, Frankfurt, GERMANY, FEDERAL REPUBLIC OF
Heer, Sabine, Radebeul, GERMANY, FEDERAL REPUBLIC OF

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2002119971 | A1 | 20020829 |
| APPLICATION INFO.: | US 2002-81642 | A1 | 20020221 (10) |

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-653685, filed on 1 Sep 2000, PENDING Division of Ser. No. US 1999-300973, filed on 28 Apr 1999, PATENTED

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | DE 1998-19818964 | 19980428 |
| | DE 1999-19917504 | 19990417 |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FULBRIGHT & JAWORSKI, LLP, 666 FIFTH AVE, NEW YORK, NY, 10103-3198
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 1193
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to new hydroxyindoles of the Formula, ##STR1##

their use as inhibitors of phosphodiesterase 4 and processes for their preparation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . and can be used for the therapy of diseases in which neuroprotection is beneficial. Such disorders are, for example, senile **dementia** (**Alzheimer**'s disease), loss of **memory**, Parkinson's disease, depression, stroke and intermittent claudication.

DETD [0097] The PDE 4 inhibiting activity is determined in enzyme preparations of human polymorphonuclear lymphocytes (PMNLs), the **PDE 2**, 3 and 5 activity with PDE from human platelets.

Human blood was anticoagulated with citrate. The thrombocyte-rich plasma in the. . . platelets are lysed by ultrasound and employed in the PDE 3 and PDE 5 assay. For the determination of the **PDE 2** activity, the cytosolic platelet fraction is purified on an anion exchange column by means of NaCl gradients and the **PDE 2** peak is recovered for the assay. The PMNLs for the PDE 4 determination are isolated by a following dextran sedimentation. . .

DETD . . . of the PDE 3 assay contain 10 .mu.M rolipram in order to inhibit possible contamination by the PDE 4. The **PDE 2** is tested using an SPA assay from Amersham. The assay is carried out in the presence of the activator of **PDE 2** (5 .mu.M cGMP).

CLM What is claimed is:

. . . pneumonia, pulmonary infiltration with eosinophilia, urticaria, ulcerative colitis, Crohn's disease, psoriasis, keratosis, pulmonary neutrophilic infiltration, chronic obstructive pulmonary disease, senile **dementia**, loss of **memory**, Parkinson's disease, depression, stroke, intermittent claudication, benign prostate hyperplasia, pollakuria, nycturia, bladder atony, kidney stone colics, and analgesic dependency, which. . .

L13 ANSWER 20 OF 106 USPATFULL

| | |
|---|---|
| ACCESSION NUMBER: | 2002:214263 USPATFULL |
| TITLE: | New hydroxyindoles, their use as inhibitors of phosphodiesterase 4 and processes for their preparation |
| INVENTOR(S): | Hofgen, Norbert, Ottendorf-Okrilla, GERMANY, FEDERAL REPUBLIC OF<br>Egerland, Ute, Radebeul, GERMANY, FEDERAL REPUBLIC OF<br>Poppe, Hildegard, Dresden, GERMANY, FEDERAL REPUBLIC OF<br>Marx, Degenhard, Radebeul, GERMANY, FEDERAL REPUBLIC OF<br>Szelenyi, Stefan, Schwaig, GERMANY, FEDERAL REPUBLIC OF<br>Kronbach, Thomas, Radebeul, GERMANY, FEDERAL REPUBLIC OF<br>Polymeropoulos, Emmanuel, Frankfurt, GERMANY, FEDERAL REPUBLIC OF<br>Heer, Sabine, Radebaul, GERMANY, FEDERAL REPUBLIC OF |

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2002115651 | A1 | 20020822 |
| APPLICATION INFO.: | US 2002-81395 | A1 | 20020221 (10) |

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-653685, filed on 1 Sep 2000, PENDING Division of Ser. No. US 1999-300973, filed on 28 Apr 1999, GRANTED, Pat. No. US 6251923

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | DE 1998-19818964 | 19980428 |
| | DE 1999-19917504 | 19990417 |

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|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | APPLICATION |
| LEGAL REPRESENTATIVE: | FULBRIGHT & JAWORSKI, LLP, 666 FIFTH AVE, NEW YORK, NY, 10103-3198 |
| NUMBER OF CLAIMS: | 20 |
| EXEMPLARY CLAIM: | 1 |
| LINE COUNT: | 1191 |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to new hydroxyindoles of the Formula, ##STR1##

their use as inhibitors of phosphodiesterase 4 and processes for their preparation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . and can be used for the therapy of diseases in which neuroprotection is beneficial. Such disorders are, for example, senile **dementia** (**Alzheimer**'s disease), loss of **memory** , Parkinson's disease, depression, stroke and intermittent claudication.

DETD [0093] The PDE 4 inhibiting activity is determined in enzyme preparations of human polymorphonuclear lymphocytes (PMNLs), the **PDE 2**, 3 and 5 activity with PDE from human platelets. Human blood was anticoagulated with citrate. The thrombocyte-rich plasma in the. . . platelets are lysed by ultrasound and employed in the PDE 3 and PDE 5 assay. For the determination of the **PDE 2** activity, the cytosolic platelet fraction is purified on an anion exchange column by means of NaCl gradients and the **PDE 2** peak is recovered for the assay. The PMNLs for the PDE 4 determination are isolated by a following dextran sedimentation. . .

DETD . . . of the PDE 3 assay contain 10 .mu.M rolipram in order to inhibit possible contamination by the PDE 4. The **PDE 2** is tested using an SPA assay from Arnersham. The assay is carried out in the presence of the activator of **PDE 2** (5 .mu.M cGMP).

CLM What is claimed is:

. . . pneumonia, pulmonary infiltration with eosinophilia, urticaria, ulcerative colitis, Crohn's disease, psoriasis, keratosis, pulmonary neutrophilic infiltration, chronic obstructive pulmonary disease, senile **dementia**, loss of **memory**, Parkinson's disease, depression, stroke, intermittent claudication, benign prostate hyperplasia, pollakuria, nycturia, bladder atony, kidney stone colics, and analgesic dependency, which. . .

=> FIL STNGUIDE

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 147.27 | 165.44 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -7.81 | -7.81 |

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| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 0.48 | 165.92 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | 0.00 | -7.81 |

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